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SYMPOSIUM

Pain and Its Relief

Special Editor
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INTRODUCTORY STATEMENT ON A SYMPOSIUM ON PAIN AND ITS RELIEF

PAIN presents us with a series of paradoxes. Few aspects of life are more widely experienced, yet pain is almost impossible for anyone to define adequately. There is great research interest in mechanisms of pain and techniques for measuring and relieving it, yet the unanimity of opinion as to goals is coupled with great dissent as to what methods to employ in the search for a better understanding of pain. Analgesics are prescribed by all doctors who see patients, yet clinicians have shown remarkably little interest in attempts to put analgesia on a sound basis, i.e., to collect reliable data on the comparative efficacy of pain-relieving drugs.

This issue of the JOURNAL OF CHRONIC DISEASES attempts to sample current thinking on pain and its alleviation. The sampling makes no pretense at being completely representative of all viewpoints, or of being a distillation of the wisest available thoughts. It does provide, in my opinion, a fairly good idea of the problems we face and stakes out the major areas of our discontent. The contributors are men who have had active interest and experience in the field; this fact, it is hoped, has produced a minimum of confabulation. Controversy has not been stifled; on the contrary, it has been positively encouraged, in the belief

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that conflicting ideas deserve open airing in the public market place. Editorial changes have been minimal; each participant is speaking primarily for himself.

Dr. Haugen records for us some of the soul-searching and intellectual concept-wrestling of a group of clinicians and research workers at a rather unique "Pain Clinic" at the University of Oregon. Their current concept of pain need not appeal to anyone else—it seems helpful to them in their daily work, and will probably be discarded if and when the concept loses utility for them.

Dr. Hardy is an important figure in the modern pain movement. He and his co-workers at Cornell University have worked hard and long on the problem of pain measurement, and their impact has been widely felt. Whether their data have great pertinence for clinical algesimetry may be debatable; that they have been largely responsible for much of the work in this field in the past decade and a half (both directly through their disciples and indirectly through their opponents) seems an inescapable fact.

Dr. Beecher, a formidable debater, takes strong issue with Dr. Hardy on many points, and the reader would do well to peruse both papers more than once in order to do full justice to each. Beecher and his colleagues at the Massachusetts General Hospital have achieved major victories in the battle against our ignorance about pain. The controlled clinical trial of analgesics in the United States owes its existence to the Harvard group.

Dr. Harris, by no means as well known as Hardy and Beecher, was chosen as still another type of investigator in the field of pain—the worker who is not completely happy with animal techniques, or clinical testing, or the Hardy-Wolff-Goodell method, and is trying to develop another technique for studying drug action in the laboratory. His paper summarizes his views on the relative merits of the different approaches.

Dr. Eddy exemplifies the remarkable persistence of a small group of dedicated souls who have tried for twenty-five years to elucidate the relationship between the chemical structure of narcotics and the pharmacologic actions of these drugs. The continuing search for nonaddicting and safer analgesics is as important as it is tedious and disheartening. The work of the Committee on Drug Addiction and Narcotics is too little appreciated by the general medical public, and I am happy for this chance to pay tribute to Dr. Eddy, his colleagues, the pharmaceutical companies who provide the Committee with funds for research, and the workers supported by this unit of the National Research Council.

Dr. Keats has supplied the superb paper expected by those who know this imaginative and perceptive worker. Starting his research on pain in Beecher's laboratory, Keats contributed greatly to the refinement and application of the techniques so well initiated by Denton and Beecher. His paper illustrates beautifully how research in a chaotic field like postoperative pain can yield data of great significance in the practical handling of patients and their distress.

Dr. Lemon has had considerable experience in the management of patients suffering from neoplastic disease. For those readers forced to deal with this challenging problem, this paper, describing multiple therapeutic avenues, should provide much assistance. Dr. Eckenhoff, too, helps in this regard. Always a careful and reliable observer, he presents in admirable fashion the potentialities and the limitations of the anesthetist in managing pain of many origins.

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It is perhaps worth nothing that four of our ten participants are anesthetists. This is no accident, but a reflection of the major role this youthful discipline is playing today in the clinical investigation of pain.

Finally, Dr. Rayport reminds us of one of the penalties we pay in return for potent analgesics. Formerly a member of the remarkably productive staff of the United States Public Service Hospital at Lexington, Kentucky, Dr. Rayport gives his analysis of the addiction problem in the use of analgesics. Although it is remarkable how little of addiction actually owes its genesis to current legitimate use of narcotics, it is sobering to have the black side of the cloud presented so ably for us.

This opening editorial has been made as short as seemed consistent with adequate introduction of the contributors to this issue. We are in their debt for a group of thoughtful and useful essays. I am sure, however, that the participants would agree with me in emphasizing that this symposium represents not so much a definitive opus as a tentative progress report.

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CURRENT CONCEPTS OF THE PAIN PROCESS

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PAIN is not a word that can be easily defined. We know what it is by past experience, but when an attempt is made to describe it, the adjectives that are used have meaning only because of their past associations. Sherrington called pain "the psychical adjunct of an imperative protective reflex"[1]—a definition which is as acceptable as any. Protective reflexes are present far down the phylogenetic scale, but we have no knowledge that animals lower in the scale than man have "the psychical adjunct." The reactions to pain in animals and their similarity to those observed in humans suggest, however, that animals, too, are aware of pain. It is interesting that dogs raised from puppyhood in a solitary, restricted environment where minimal opportunity for painful experience exists do not act as though they feel pain when subjected to testing in early maturity.[2] What they feel seems to have no meaning to them, and even what Sherrington terms "an imperative protective reflex" is absent in most such animals. Avoidance of a painful stimulus is learned, but it takes many trials before anything like conditioning develops. This would indicate that even in simple acts of avoidance the process is more complex than a simple stimulus and response and must include a patterning within the brain. The influence of past experience and learning is evident in any group of patients as one observes the notable differences in their reactions to stress and pain.

What, then, do we know about pain? Up until the middle of the nineteenth century, the concept of the philosophers was accepted. Pain was the antithesis of pleasure and the equivalent of "unpleasantness." Then came the "law of specific nerve energies"[3] which can be interpreted to mean that each sensory quality has its own specific sensory unit. The development of this concept has continued into the present day, and upon it is based most of what we have been taught about the sensations. It is the purpose of this paper to review that concept as it pertains to pain in light of recent investigations. It is also our purpose to present an idea of the functional organization of the central nervous system that has been of help to our study group in understanding some of the bizarre patterns of pain one sees in practice.

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Most of the evidence for pain being a separate and distinct sensation like the sensations of light, smell, or hearing has come from studies of the peripheral receptors. Histologists and physiologists have long been intrigued by the variety of these units found in the human skin. Evidence for and against a separation of skin sensation into the four modalities—heat, cold, touch, and pain—each with its own receiving unit, is still weighted in favor of the specificity of the receptors in most textbooks on the nervous system. Readers are familiar with cross-section drawings of skin showing Paccinian and Meissner corpuscles, end bulbs of Krause, Ruffini's end organs, and the "undifferentiated" or "bare" endings. Their morphologic differences suggest that they subserve special functions. It may be that stimuli of a certain type or intensity activate one more readily than another; but recent work by Sinclair, Weddell, and Zander casts new doubts on the general theory, and it will be interesting to observe the effect of their contribution on future teachings. In their studies of the human pinna[4] they found but two identifiable types of receptors: a basketlike network around hair follicles, and the familiar bare undifferentiated ending. With carefully controlled studies, they were unable to determine any difference in the ability of a test subject to discriminate heat, cold, touch, or prick in the skin of the ear from that of the skin of the forearm where all previously described cutaneous receptors are found. In their words: "It therefore appears that the current theory of cutaneous sensation, which demands specific receptors for each modality of sensation, cannot be of universal application to the human body, and thus its standing must be seriously called in question."

Another recent report is by Tasaki and his co-workers,[5] using the toad and cat as experimental animals. They have been studying the action currents in single afferent nerve fibers, myelinated and unmyelinated, elicited by stimulation of the skin, thus hoping to clarify the physiologic properties of the various sensory nerve endings. Their results seem to indicate that more than four types of endings are present, and that more than one type of stimulus will evoke an impulse in a single nerve fiber. It is their belief that a mechanical or noxious stimulus to the skin will set up impulses in more than one type of afferent fiber, and that "our 'pain' or 'pressure' sensation is aroused by the concurrent activity of several different kinds of sensory units."

Hardy, Wolff, and Goodell[6] have advanced the concept that the total pain experience is composed of the sensation of pain plus associated sensations (such as heat, cold, or pressure) with an overlay of emotional and affective states (fear, apprehension, etc.). They believe, after years of study, that the pain experience can be separated into two component parts—the perception of pain, and the reaction to it. They base their conclusions on the results of their experiments using the dolorimeter. This instrument uses a 500 watt incandescent lamp as a source of heat, and the light from the lamp is focused by a condensing lens through a fixed aperture on a blackened area of skin. Flexibility in control of the amount of heat reaching the skin is provided by a rheostat and timing device. They found that most subjects perceived pain at approximately the same intensity of heat—a point at which the heat "swelled" to a distinct sharp stab of pain at the end of a three-second exposure. They conclude that an average threshold for pain can be determined quite objectively provided the subject

can maintain a detached, unprejudiced attitude and can concentrate on the experiment. Threshold pain, according to this group, is at the point of tissue damage, and constitutes the perception referred to above.

Continuing their work with the radiant heat method, Hardy, Wolff, and Goodell propose that the dimensions of pain also can be determined in trained subjects without involving the second component—reaction. The dimensions of intensity have been studied from threshold to the maximum pain beyond which no further discrimination can be made. It is concluded that there are twenty-one perceptible gradations between threshold and ceiling pain, and a "dol" scale has been devised by combining two of the just noticeable differences in intensity. They are hopeful that the "dol" scale will prove to be of value in determining objectively how much pain a patient is suffering, as for example, during labor and delivery. In trained subjects, they write, "pain sensation can be isolated as an entity to be focused upon for special analysis." It is their belief that pain sensation itself is no different from other sensations in that it bears a highly predictable relation to the intensity of the stimulus, and, like other sensations, it is mediated by specialized neural equipment.

Several investigators of pain phenomena have been unsuccessful in their attempts to obtain consistent results with the dolorimeter technique. Our pain study group was among these.[7] We were interested in utilizing the method in our pain clinic, hoping to obtain objective information on the amount of pain our patients suffered. Before we began testing patients, we wished to gain experience ourselves, and after more than one hundred hours of testing each other over a period of a year, we concluded that the pain threshold was relatively constant as determined by the dolorimeter under the conditions prescribed by the originators of the technique. However, we could not become proficient enough to confirm the "dol" scale of intensities from threshold to ceiling pain. We doubt that "perception" and "reaction" can be anything but psychologic terms. It is to be expected that there is more agreement between people on how much heat causes barely perceptible pain than on how much of thermal pain they can stand, but "reaction" must play some part in the interpretation of any sensory experience. To hold otherwise, we would have to postulate some raw sensation of pain apart from any meaning—a "signal" arriving centrally that could be perceived, even judged in intensity according to the strength of the stimulus, without being affected by any of the accumulated patterns of reaction developed from past experience.

So much of past physiologic investigation of sensory mechanisms has been directed toward a study of the peripheral receptor, becoming bound in the rigidity inherent in the concept of four modalities, that it is refreshing to observe the trend toward a study of the patterning of the impulses in nerve fibers. This trend has been made possible by the improvement in electronic recording equipment. We now prefer to view the receptor simply as a sensory unit which in some way must impart a pattern to the nerve impulses evoked by its stimulation. This patterning will be influenced by fiber size, their stimulus characteristics, by the state of excitability peripherally and centrally, and by a number of other factors. We should bear in mind that the sensory system exists solely to prepare the organism for motor action, and that many patterns of response occur within the central nervous system besides the one that produces awareness of sensation.

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Among the noteworthy contributions to our knowledge of how the central nervous system works, coming as a result of the development of the cathode ray oscilloscope, was the work of Gasser and Erlanger[8] in correlating nerve fiber diameter with the rate of conduction, and their later contributions on the allocation of function to the various velocities. They and Heinbecker, Bishop, and O'Leary[9] have given us direct evidence of the association of pain impulses with the C fiber, and the delta group of the A fiber. Another important concept relating to the functioning of the central nervous system was presented by Lorente de No,[10] who demonstrated with convincing evidence that facilitation at cord level is explained by activation of internuncial neurons and of rotation of activity within the internuncial "pool" of circuits.

This, very briefly, has been the background of the knowledge of pain mechanisms. When one attempted to apply these concepts to the variety of problems met in clinical practice, where chronic pain states often defied cure, it was increasingly apparent that much of what had been written did not fit the picture. The first of the clinicians seriously to attempt an analysis of the discrepancies was Livingston.[11] It was his expressed opinion that important as the contributions had been in providing stepping stones to a new concept of the physiology of the central nervous system, the work was still not at a stage where it could adequately explain such states as causalgias or phantom-limb pain. The pain study group which he heads has evolved a way of thinking of the functional organization of the central nervous system that we wish to outline here. Most of what we offer is not new, nor is the way in which concepts are correlated particularly unique or at variance with the thinking of many neurophysiologists; but the application of these concepts to the mechanisms of pain may offer the clinician a working basis for understanding some of the perplexities associated with chronic pain states.

To introduce our point of view, we must first briefly review the customary way of thinking of the organization of the nervous system. We usually think of functional levels, one above the other, with the spinal cord lowest and the frontal lobes the highest point of development. We have learned from comparative anatomy how this development has occurred in the transition from lower forms to man. For most of us, the organization resembles a series of horizontal compartments, each dominant over the one below, the compartments being from below upward, the spinal cord, the medulla, the subcortical centers, and the cortex (Fig. 1). The functional unit from which all action patterns are built is the simple reflex, as exemplified by the two neuron arcs in the cord. The medulla, in this concept, controls automatic vital functions and is in turn controlled to a degree from higher centers in the hypothalamus. The subcortical levels, acting much in response to sensory input, regulate massive responses, controlling the autonomic nervous system, and at thalamic levels are thought to be the seat of primitive emotion and affect. Perception of pain has been placed at this level. Over all these is the cortex reaching its highest development in man. Throughout the length of this system, all sensory modalities project to the cortex, and from its motor areas comes more or less specific control of lower motor mechanisms. The top role in this hierarchy is assigned to the frontal lobes.

Our study group does not suggest that all this is wrong. It believes, however, that we can become so fixed in our way of thinking that we may forget that the central nervous system is a dynamically plastic functional whole, and that even the simplest reflex acts are very complex, involving unknown numbers of neurons in addition to the demonstrable two-neuron arcs. This is the same objection we have to the concept of specificity. It is not that we do not believe there is some type of specificity in peripheral sensory units, but that too much emphasis on specificity decreases our ability to recognize the importance of the patterning of nerve impulses evoked by stimulation. Most of us have constructed a bell-ringing telephone switchboard concept of central nervous system function, and if we see pain cases that do not fit the picture, we tend to blame the patient or his imagination.

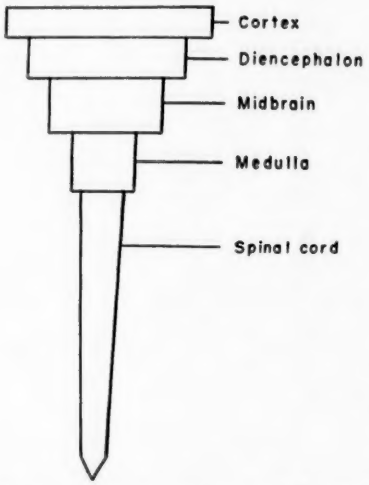

Fig. 1.—The hypothetical "horizontal" compartmentation of the central nervous system as it relates to transmission and perception of pain.

On the basis of several years of study and discussion in our seminars, our group has assumed that "pain" is a sensory perception, a subjective psychologic experience in which "awareness" is an essential element. In other words, we are unwilling to call anything pain unless it is "felt" as such. We do not believe that it is a physical quantum that can be measured in terms of stimulus intensity or in terms of reflex responses. On the other hand, "perception" must have an anatomic substrate, for mentation is a function of the brain. The body functions as a single unit, and anything that upsets the body's equilibrium, as, for example, disease and pain, must set in motion a chain type of reaction in an effort to achieve homeostasis, the central nervous system being involved as much as any organ.

In recent years, neurophysiologists have been able to study some of the complex interactions which can take place within the central nervous system of anesthetized and unanesthetized animals. Areas which are silent under anesthesia have been found to be very active in the "awake" preparation. Attention has shifted to such little understood regions of the brain as the association areas and the reticular formation. The contribution of Lorente de No on the inter-

nuncial neurons paved the way for much of the recent work. Here was demonstrated, in the neuronal pool interposed between the sensory and motor components of the cord, a means by which temporal and spatial dispersion of input could take place. The number of neurons making up the pool permits great variety in dispersion patterns from simple to complex. From his theory of a closed, self-re-exciting chain within this pool, came the concept of self-sustaining pain patterns as exemplified by causalgia. It has also become clear, as results of research are made known, that influences from any part of the central nervous system can alter the motor response to a sensory stimulus. Studies of the reticular formation in the midbrain and medulla demonstrate that it plays an important part in modifying activity within the internuncial pool. The midbrain reticular formation, when stimulated, also has been shown to have an alerting effect upon an anesthetized animal's electroencephalographic tracing. This response persists even when the classical sensory pathways have been destroyed at approximately the same level as that at which the stimulus is applied. If the reticular area is destroyed, no amount of stimulation will alert the animal as judged by its cortical electroencephalogram. Magoun and his co-workers[12] suggest that the reticular formation is very important to the awake state, and that it receives collaterals from the main sensory and motor tracts.

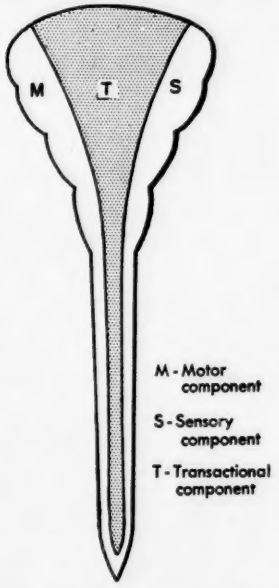

Fig. 2.—The hypothetical "vertical" organization of the central nervous system as it relates to transmission and perception of pain (see text).

It appears that there are two pathways for the sensory input and two for the motor output. The main sensory and motor pathways provide a rapidly conducting system, and the collateral system through the reticular formation provides a slower conducting diffusion pathway by which "information" from many sources can be modulated and integrated.

This suggests to us a vertical organization[13] of central nervous system function (Fig. 2). The classical sensory and motor pathways from cord to

cortex are indicated as separate vertical columns, with an area between, which we have called the "transactional" component. The "transactional" component, in this hypothesis, includes the internuncial pool, the collateral pathways in the reticular formation, some of the medially placed nuclei of the thalamus, and the association areas of the cortex. We do not consider this diffusion system to be an amorphous mass of undifferentiated cells. On the contrary, we consider it to be patterned as a result of learning and experience so that the motor response will be appropriate to the stimulus. There are strong indications that "awareness" has its anatomic substrate within the reticular formation, for here there is fusion of input from several sensory modalities with positive evidence of their interaction. In this concept, the autonomic nervous system is considered in no way different in organization from the somatic sensory and motor systems. We do not venture to postulate further than this, but it seems reasonable to consider "memory" within the transactional component.

To summarize, this concept of organization merely offers a way of thought regarding the functioning of the central nervous system. By visualizing a transactional component interposed between the sensory input and motor outflow, in continuity from "top to bottom," we view the working of the nervous system more clearly as a functional whole. We can see how the entire patterning of a complex subjective sensation like pain may be altered by normal or abnormal activity within this diffusion system, so that what the patient reports to his physician no longer needs to "conform" to older concepts to be valid.

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LIMITING FACTORS IN EXPERIMENTAL PAIN

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JUST as the existence of pain and possibilities for its treatment constitute probably the most ancient reasons for the existence of the physician, so also this antiquity has led to an accumulation of folklore around the subject. With the extraordinary development of experimental medicine in the nineteenth century, it is not surprising that the important problems of pain and its treatment were also subjected to experimental attack. Many of the results of this have been good indeed; some are open to adverse comment. The experimental approach has continued down to the present, and work in this area has been especially lively in the last fifteen years. As Macdonald[34] has pointed out, much of the limelight in therapeutics in recent years has been focused on chemotherapy; but it is nonetheless true that much of medicine is still concerned with the treatment of symptoms, and of these the most important is pain. There is an instant need for relief of pain.

As in all vigorously studied areas, partisanship has reasonably enough emerged, with egos involved in this or that view. Even the role of a commentator is a perilous one, likely to lead at the very least to strong letters to the editor; so in the interest of impartiality, certain principles will be set down as guides in the hope that on this basis judgments can be fairly made. Principal attention in this paper has been given to pain experimentally contrived in the laboratory as distinguished from the pain of disease or trauma.

GENERALIZATIONS CONCERNING PAIN IN MAN

The generalizations will be stated here and then documented and discussed in the sections to follow.

The original sensation and the reaction to sensation are the components of pain. One of the few things all hands seem to be agreed upon is that the 60-year-old concept just stated is a useful one. In its modern form at least, it goes back to a book by Marshall,[38] *Pain, Pleasure and Aesthetics*, published in 1894, but more especially it goes back to an address delivered by Strong[50] in 1895, in which he first formulated the view presented here that pain consists of these two ele-

ments, the original perception and the psychic processing of this original sensation. These two elements appear to be essential parts of the pain experience.

One step beyond the bare statement of the concept and a confused and confusing area is entered, more confusing than is perhaps necessary. Many writers, while endorsing the concept as stated, have various and decided views as to what constitutes the reaction phase. To one, it is the withdrawal of a burned finger from a flame; to another it is change in the galvanic skin reflex produced by alteration in circulation or by sweating; to still another it is flight, and so on. I submit that such phenomena are the *consequences* of pain and in that sense a reaction, *but they are not pain.*

There are, however, as we shall see, sound reasons for considering the psychic reaction or processing of the original sensation as an actual part of the pain experience. For example, block of this form of reaction can stop suffering, can leave the patient unaware of pain. This is not true of the other forms of reaction just mentioned. This is the basis for what might otherwise seem like a baseless and arbitrary choice: the unconscious psychic reaction or processing of the original sensation appears to be an essential component of the pain experience. Attention in this paper will be focused on this form of reaction.

The perception component is determined by stimulation of the pain apparatus and by impulses that travel over it to consciousness. It is determined by intensity of stimulation and possibly by duration and extent, although Hardy, Wolff, and Goodell[20] have presented interesting evidence that there is no spatial summation of pain with the radiant heat technique of stimulation. It is important to recognize, as Wikler[53,54] and others have shown, that the original sensation probably reverberates in the nerve nets long before it erupts into consciousness. The physical requirements are available for long-circuiting of nerve impulses through internuncial neurons. In short, the processing of the psychic reaction to the original sensation undoubtedly begins *before* awareness of the sensation has been achieved (Beecher[7]). Presumably, the original sensation is the same for all individuals and depends chiefly on intensity of stimulation. As soon as processing begins, it loses that sameness and is no longer a pure perception, surely not by the time it emerges into consciousness.

The reaction or processing of sensations that travel over the peripheral pain apparatus and emerge in consciousness is determined by past experience, by conditioning, by memory, by judgment, by present meaning of the pain. This reaction is never alike for any two individuals and, indeed, with the passing of time and accumulation of life experience, is never exactly the same for the same individual from one time to another.

THE PAIN THRESHOLD IN MAN*

The Inconstancy of the Pain Threshold as Studied by Three Methods.—Chapman[13] found, in studying the pain threshold in 200 normal subjects by the radiant heat method of Hardy, Wolff, and Goodell, that the threshold varied much more

*A very much fuller discussion and documentation of the technical matters mentioned here is in preparation for *Pharmacological Reviews.*

widely, −40 to +50 per cent, than did Hardy, Wolff, and Goodell,[20] who found the variation to be ±12 per cent of the mean. Schumacher, Goodell, Hardy, and Wolff[45] found a standard deviation of only ±1 per cent for a group of 150 persons. Several others failed to confirm these workers as to the constancy of the pain threshold in man, using the radiant heat technique: Schamp and Schamp,[44] Clausen and King,[14] Slaughter and Wright,[48] and Leduc and Slaughter,[33] to mention a few.

Using electrical stimulation of the skin, investigators have found wide variation in the pain threshold in man: Pfeiffer, Sonnenschein, Glassman, Jenney, and Bogolub[43] report this; Martin, Grace, and McGuire[39] found considerable variation. Lanier[32a] found about 50 times as much variation in normal human subjects as the Hardy group did. Parsons and Goetzl,[41] using electric shocks to teeth, found a very wide spread of the pain threshold in man.

Seevers and Pfeiffer,[46] using a modification of the von Frey hair technique, found that the pain threshold varied widely from man to man.

As recently as 1951, Wolff and Wolf[58] said, "The available evidence from studies with various devices indicates that all persons whose bodily structures are healthy have approximately the same capacity for perceiving pain. Under normal conditions this threshold does not vary from day to day." It appears to be necessary on the basis of the available evidence to conclude that Hardy and Wolff and their associates were in error in their belief that the pain threshold is a fairly constant characteristic of man.

Pain Threshold and Analgesic Action.—A great impetus was given to the study of analgesic agents by the historic paper of Hardy, Wolff, and Goodell,[20] where they presented graphs showing extensive elevations of the pain threshold by analgesic agents. They even showed apparently clear differences in curves with as little as 0.03 Gm. of acetylsalicylic acid (Wolff, Hardy, and Goodell[57]). It would be a great mistake to underestimate the importance of the work from this group. At the same time, certain questions must be raised. Their work, first presented in 1940, redirected attention to the possibility of measuring the effect of analgesic agents and unquestionably stimulated a vast amount of interest in the field. Their beautiful curves perhaps oversold their method, for even to the present time new workers are constantly entering the field without ever asking questions as to whether in fact there may be any dependable relationship between analgesic action and pain threshold change in man. Fortunately, such a trying statement does not need to be left to one man's opinion. The record may be consulted.

It is true that Hardy, Wolff, and Goodell have repeatedly pointed out that reaction to the original sensation may be more greatly altered by a narcotic than the pain threshold. Nevertheless, a principal purpose of their method had been to show in graphic terms the power of an analgesic agent to elevate the pain threshold. They say that below the ceiling of analgesic action "the effect on the pain threshold (is) proportional to the amount of drug used." They say, "The common analgesics in addition to *effectively raising the pain threshold* [italics mine] also have a major function in changing reactions, attitudes, feelings" (Wolff and Hardy[56]). They have reported this change in pain threshold with

the administration of analgesic agents in many experiments performed under routine conditions; and so have those who have come after them. Scores of examples from the work of many men with various pain-producing techniques could be given to illustrate their view that analgesic agents do, according to them, elevate the pain threshold. Harris and Blockus[22] state the prevailing view: "To validate an algesimetric procedure it should be demonstrable that a compound generally acceptable as a clinical analgesic will cause the threshold of experimentally induced pain to become higher than it might otherwise be if no treatment or a placebo had been given." Harris and Blockus have even gone so far as to deny that acetylsalicylic acid is in any proper sense an analgesic because in their hands the drug did not produce in man an elevation of the pain threshold to electric shock stimuli. With this as a background, some of the comments shortly to be presented may seem odd. It is to be emphasized that this part of the paper deals only with the pain threshold in man. Animals are another matter.

It is apparent that many observers have never had the slightest doubt of a relationship between analgesic action and pain threshold elevation in man. It can be said in passing (the crucial point will be documented in detail in the long review already referred to) that the design of the experiments of the originators or of those who have confirmed them has not been reassuring in many cases. The same can also be said of several of those who have failed to confirm them, but, in general, the opponents have had better designed experiments than the advocates. Here is a partial list of those who have failed to confirm Hardy, Wolff, and Goodell's observations of a relationship in man of pain threshold rise to analgesic action. A number of the following groups used "trained" subjects, so it is difficult to accept Wikler's[55] view that trained subjects are useful whereas untrained are not. Even the Hardy, Wolff, Goodell group are not consistent in requiring training as essential. Of the numerous examples of such inconsistencies, one can mention the statement of Wolff, Hardy, and Goodell[57] that "this threshold pain was easily recognizable even by untrained subjects." Yet they (Hardy and Cattell, 1950) say, "It is concluded that untrained subjects [160 medical students], even of high intelligence, cannot be used successfully to measure the threshold raising effects" of various analgesics. On the other hand, in discussing dol scale determinations (which they are agreed require "much more in the way of concentration than did the measurements of pain thresholds") they say that in this difficult field the untrained students gave data "approximately the same as that obtained with experienced observers."

The following have failed to confirm Hardy, Wolff, and Goodell's observations with the radiant heat method of stimulation in man: Andrell,[2] Flintan and Keele,[17] Haugen and Livingston,[24] Jackson,[30] Kuhn and Bromily,[32] Whyte,[52] Birren, Schapiro, and Miller,[10] Isbell and Frank (quoted by Wikler,[55]), Denton and Beecher,[15] Thorp,[51] Dodds, Lawson, Simpson, and Williams,[16] Andrews,[3] and Slaughter[47] reported that both he and Chapman had found some individuals, judged by this experimental pain method, to be "congenitally refractive" to 8 mg. of morphine. The writer is not aware of any clinical counterpart of this finding.

The following have failed to confirm Hardy, Wolff, and Goodell's observations with the electric shock-to-teeth method of stimulation in man: Harris and Blockus,[22] Harris and Brandel,[23] Sonnenschein and Ivy,[49] Ivy, Goetzl, and Burrill.[29] These last investigators reported that following the administration of 16 mg. of morphine subcutaneously, 7 out of 16 subjects showed a fall of pain threshold rather than a rise, in 1 there was no change, and in only 6 a rise. Two were unaccounted for. It is a remarkable fact that these investigators apparently still rely on their method.

The following have failed to support Hardy, Wolff, and Goodell's observations with the von Frey hair technique (or a modification of it) in man: Mullin and Luckhardt[40] and Seevers and Pfeiffer.[46] The latter group reported that some individuals (with low pain thresholds) showed no effect from opiates.

Batterman and Himmelsbach[5] state, somewhat paradoxically perhaps, that pain threshold changes are of "minor importance" as far as analgesia is concerned; yet, they say, they are of "immense help" in evaluating the relative potency of analgesics! I am unable to understand this.

Further evidence of the unrelatedness of pain to pain-threshold change in man and analgesic agents was described by Houde, Rasmussen, and LaDue[27] who told of a patient who, despite a great elevation of pain threshold by an analgesic agent, nonetheless had a return of pain in the region of his disease at the height of the pain threshold reaction.

Parsons and Goetzl[42] "feel" that "a drug may possess analgesic properties in spite of its failure to raise the pain threshold in normal human subjects." This might be called a kind of internal heresy, for Goetzl's considerable series of papers has been dedicated to the proposition that analgesic power can be revealed by pain threshold elevation in normal human subjects.

Andrews[3,4] reported that the threshold-raising effects of morphine in post-addicts was greatly reduced in comparison with such effects in normal man, yet modest doses of morphine relieve pain in the post-addicts.

Cattell[12] has said, (and he speaks as a member of the Cornell group): "The rise in (pain) threshold which may accompany analgesia must be looked upon as incidental to the changes in mental function, with awareness of pain not necessarily altered." This is not in line with the group's insistence that the pain threshold findings are a measure of the original sensation, not complicated by the reaction component. Gold, in commenting on Cattell's remarks, said, "Several laboratories have now begun to compare analgesic agents by their power to raise the (pain) threshold. There should soon arise a classification of analgesic agents based on their power to raise thresholds." But then he continues with his usual wisdom, "I have the notion that such a classification, however, would not match the classification based on clinical experience in the relief of pain. A small dose of morphine which does not raise the threshold any more than a large dose of aspirin is much more effective in relieving pain than the large dose of aspirin."

From the Hardy, Wolff, and Goodell group comes the statement (Hardy, Potelunas, and Meixner[19]) that while apomorphine greatly reduced the pain intensity of a woman in labor, it had no effect on pain threshold. Evidently, then, they agree that pain relief can occur without threshold change.

Surely, the many foregoing examples are sufficient to cast doubt on the existence of any dependable relationship between the effect of analgesic agents and the pain threshold, as well as doubt on any relationship between experimental pain threshold and pain suffered by a patient.

The "Purity" of the Pain Threshold in Man.—Hardy, Wolff, and Goodell have long advocated the view that the pain threshold represents "perception" of pain, ". . . that the threshold for the *perception* of pain under normal circumstances is approximately the same in all subjects and in the same subject at varying times of the day" (Wolff and Wolf[58]). In a foregoing section, sample data were given to indicate the notable lack of confirmation of this often-stated view, not only with their own radiant heat technique but by other methods as well. As recently as 1953, Hardy, Wolff, and Goodell have reaffirmed their belief in the separability of pain sensation, i.e., pain threshold, from associated reaction patterns.

Enough data were cited in the preceding paragraphs to indicate the inconstancy of the pain threshold in man. In my view, this inconstancy is probably to be explained by "contamination" with reaction component of what doubtless started out as a pure perception. There is good anatomic evidence for this view in the nerve nets in the spinal cord. Individual nerve fibers have wide ramifications with conducting apparatus of great extent. Several fibers innervate each "pain" spot and these may supply other spots as well. Pain reactions are based upon at least a three neuron arc with one or more neurons in the gray matter (Adrian[1]). Wikler[53,54] showed that both morphine and methadone when tested in spinal cats and dogs consistently depressed only those hind-limb reflexes which are characterized by considerable afterdischarge, and did not depress, but actually increased in some cases, those hind-limb reflexes that had little or no afterdischarge. Wikler, therefore, concluded that the site of action of these drugs was on the internuncial neuron system of the spinal cord.

The variability of the pain threshold from man to man and within a given man from time to time, as indicated in a preceding section, may well be accounted for by the reaction or processing component influencing the pain threshold.

THE REACTION OR PROCESSING COMPONENT IN MAN

From the data presented in the foregoing sections, it can be seen that there are extensive reasons for doubting in man: (a) the constancy of the "normal" pain threshold, (b) its purity as a perception, and (c) its responsiveness to the action of powerful analgesic agents. The evidence is somewhat conflicting, but the sound conclusion can be drawn that where there is such great failure of careful workers to agree, the facts are not as clear-cut or as evident as they have seemed to some investigators. The failure to establish a clear relationship between pain and threshold under analgesic agents in man provides a negative kind of evidence that since these compounds are undoubtedly effective in relieving pain, they act on the other principal component of the pain experience, namely, the reaction.

This matter need not rest on negative evidence, for there is a considerable body of positive support for the view that the reaction component is the site

for the action of drugs which modify subjective responses. The demonstration of this requires the use of pain of pathologic origin. Such discussion is beyond the scope of this paper, except as it supports the usefulness of the dichotomy, experimental versus pathologic pain. Beecher[7] has summarized considerable evidence for the importance of the reaction component as the site for the effective action of analgesic drugs. In brief, effectiveness of emotion in blocking pain (euphoria, or anger in combat) is a telling argument for it; so also is the significance of the wound in determining the pain experienced (Beecher[8]), the powerful effect of placebos (Beecher[6]), and the evidence for the greater effectiveness of placebos in the presence of increased stress (Beecher[9]).

In the relationship of the reaction component to effective drug action, we can see a reason for the difficulties of demonstrating, experimentally, dependable effects of narcotics on the pain threshold of man: it is difficult, if not impossible, to reproduce in the laboratory the reaction component produced by the pain of disease or of trauma, although important facets of this have been usefully contrived. Just as evidence has been given (Beecher[8]) that the significance of a serious wound determines to a dominating degree the development of pain, so also is it not usually possible to reproduce such significance in the laboratory. This has imposed a very great limitation on experimental pain to the present time. In so far as it becomes possible to reproduce in the laboratory an important reaction component, the breadth and usefulness of experimental pain will increase. Sound work in this direction is already a matter of record. The importance of anxiety in the appearance of pain and its relief by morphine has already been indicated by the experimental pain work of Malmo and Shagass[35-37] and by the fascinating work on this subject by Hill, Kornetsky, Flanary, and Wikler,[25,26] and by Kornetsky.[31] Their conclusions, based on experimental work as to the importance of mood in determining the outcome, are supported by Beecher's[8] work with mood as a determinant of pathologic pain.

THE "PAIN" THRESHOLD AND REACTION IN ANIMALS

While this matter will be considered in great detail in the "Review" in preparation, this is not necessary here, for all careful workers are in essential agreement: The "pain" threshold *is* in most cases dependably responsive to the action of *powerful* analgesic agents in animals, but most investigators have not been able to show a dependable relationship with agents of the acetylsalicylic acid order of analgesic power. The word *pain* is used in quotation marks since the conclusion is only presumptive that pain is produced in animals by the various forms of stimulation employed. Unquestionably, the radiant heat method of stimulation developed by Hardy, Wolff, and Goodell has not only given a tremendous impetus to work on animals, but it remains probably the most useful method for work on them. Certainly, their method has been the most widely used and the most carefully studied. Their achievement in this area is a very great one.

The question can be raised as to why there is a difference between man and animals. In the first place recognition should be given to the fact that very different parameters establish thresholds for the two groups: in man it is de-

termined by the brain cortex, and in animals by reflex phenomena, and usually spinal reflexes at that. In the second place, the response in animals is evidently a *reaction* to pain, not in any sense a perception. (In man, it was seen that the pain threshold represented perception plus probably varying amounts of the reaction factor, believed to account for the threshold's erratic behavior.) In the third place, experimental pain in an animal is comparable probably to pathologic pain in man. There is no question that pathologic pain is dependably responsive to analgesic agents and probably because of the great reaction component contained therein. Everybody who has received morphine because of pain arising from disease or trauma knows how dependable the drug is. Beecher[7] has summarized the evidence that analgesic agents act on the reaction component. All pain, experimental or pathologic, is serious and significant to an animal, since it cannot differentiate as man can, and powerful analgesic agents are effective probably because there is a large and fairly constant reaction component in the animal's response.

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SOME RESULTS OF THE USE OF EXPERIMENTAL PAIN

Desirable.—Much of the work of recent years which has led to the establishment of pain as a specific sensation (not an overstimulation of touch, for example) with its own anatomic apparatus has depended upon the use of experimental pain both in man and in animals. Experimental pain has made possible interesting attacks on such basic questions as spatial summation of pain. Development of experimental pain methods has led directly to the development of ingenious and quantifiable methods of stimulation which are applicable to studies of other modalities—touch, warmth, cold, and so on. Such methods have greatly stimulated the study of pain itself.

The use of experimental pain to attack the components of the pain experience has already been rewarding in studies of the role of fear and anxiety in relationship to the development of pain and in understanding its mechanism of relief by drugs. This work has already indicated that experiments can be devised which will help to clarify "perception-reaction" relationships. Much more can be expected in this same direction with resulting increased insight into the meaning and control of the very important reaction component.

Experimental pain *in animals* is useful (but not an infallible guide) for the appraisal and comparison of analgesic agents.

Undesirable.—A mistaken reliance on the responsiveness of the experimental pain threshold to the action of analgesic agents has led to denial of common observation, for example, that acetylsalicylic acid is an analgesic agent. Experimental pain thresholds in man have been misused and erroneously depended upon for evaluating analgesic agents. They have been misleading. This has led repeatedly to illogical statements by those who have been forced to agree that pain threshold changes after analgesics in man are minimal, but who yet insist that these changes are of "immense" value in screening analgesic agents. One must conclude that experimental pain in man is not useful for the chief purpose to which it has been put: the comparison of analgesic agents.

While it must be agreed that the "pain" threshold in animals is more dependable than, and a very different thing from, the pain threshold in man, and while it is generally responsive to the effects of powerful analgesic agents, it has been known to fail in the evaluation of some narcotic agents, as with N-allylnormorphine. It has also usually not been responsive to the action of the acetylsalicylic acid class of compounds. Rigidity of interpretation has led to error in animals, as in these instances, and to error in man.

CONCLUSIONS

1. The studies of many reliable investigators indicate that the "normal" experimental pain threshold is neither constant from man to man, nor is it constant in a given individual from time to time.

2. The pain threshold varies widely. This is probably because it does not represent a pure perception. This is an inference based upon its variability; on the anatomic and physiologic evidence that "processing" of it (reverberation in the nerve nets) occurs at a spinal cord level at the least, and probably higher in the central nervous system, before awareness has been achieved; and finally on the fact that experience and value judgments (conditioning) enter into the determination of the pain threshold.

3. The available data are sufficient to indicate that there is no regularly dependable relationship between analgesic action and the experimental pain threshold in man. There is reason to doubt that there is any reliable correlation between experimental pain threshold level and suffering experienced by a patient.

4. The psychic reaction or processing component in man is the principal site of action of analgesic drugs. This follows since the "perception" component is not dependably altered by these agents in man. The evidence for this does not rest solely on exclusion, but is supported by the clearly demonstrated effectiveness of "pharmacologically" inert placebos. The conclusion is also supported by the effectiveness of mood in determining or blocking the pain experience, and by the fact that the attitude of the subject and the significance of the wound can determine the presence or absence of pain.

5. The "pain" threshold in animals is dependably elevated by most powerful analgesic agents. Recognition should be given to the fact that pain threshold in man represents a value judgment of the cortex, whereas "pain" threshold in animals is in almost all cases a reflex *reaction* to presumed pain, and generally a spinal reflex. Thus the two parameters are very different. It is not surprising that study of these different things leads to different conclusions.

6. Experimental pain has wide usefulness in man and in animals. It has often been misused, especially in man.

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THE NATURE OF PAIN

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THE desire to investigate pain sense and to evaluate its role in human life is an ancient one. Aristotle,[1] two and one-half millenia before our times, states in his *Nicomachean Ethics*, ". . . we measure our actions . . . by the rule of pleasure and pain. For this reason, then, our whole inquiry must be about these. . . ." Speaking of pain in this broadest sense and its natural opposite, pleasure, he conceives of the two as being the basic moral drives guiding men's actions. Thus, he writes, "for moral excellence is concerned with pleasures and pains. . . ." It is probable that these ideas were ancient even in the time of the great Greek philosopher because in the third chapter of the book of Genesis, is is noted that God said to Eve after the eating of the forbidden fruit: ". . . I will greatly multiply thy sorrow and thy conception; in sorrow thou shalt bring forth children. . . ." One begins discussions of pain with Aristotle because he was further concerned with all the senses of man. These he divided into the five classic categories of vision, hearing, smell, taste, and touch. Pain was not included among the senses because it was considered to be a "quale of the soul," a state of feeling, and the epitome of unpleasantness. Aristotle was aware of the sensory nature of bodily pain and of its close relation to injury, but he preferred to include this aspect of pain in the broader concept of pain as a moral force; he emphasized that ". . . virtue . . . is concerned with pleasures and pains. . . ."

The undoubted usefulness of this conception of pain has guided man's actions in respect to bodily pain from earliest time. Not only was the judgment of God for the committing of the original sin cast in this framework, but so too have been the actions of rulers of States and others in authority toward those convicted of crime. Undoubtedly, much thought has gone into devising means of producing pain in the interest of group justice.

Two thousand years after Aristotle, the matter of pain was again thoroughly discussed in relation to the other senses. John Locke[2] who felt that ideas can approach our minds only through sensation or reflection, classified pain as an

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idea composed of both sensation and reflection. He, like Aristotle, felt that pain was best considered as the opposite of pleasure. He wrote in his *Essay Concerning Human Understanding*, "By pleasure and pain, I would be understood to signify whatsoever delights or molests us; whether it arises from the thoughts of our minds or anything operating on our bodies." He, too, was aware of the sensory nature of pain and its relation to the effect of injurious agents on the body. For example, he notes, ". . . yet an excess of cold as well as heat pains us. . . ." However, he felt it more profitable to think of pain in the Aristotelian main sense when he stated, "Things then are good or evil, only in reference to pleasure and pain." He, too, could not consider pain a sensation such as sight or hearing because these latter had a neutrality to the perceiver that was not possible for pain perception. For example, the hearing or the seeing of an event might cause either pleasant or unpleasant feelings, but bodily pain was always injurious and unpleasant—it was never neutral.

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It is doubtful if, today, there has been much added to the philosophic formulations concerning pain, and our attitudes toward the sensation have certainly sanctioned it as a tool by which parents, the community, and the State guide the conduct of the individual throughout his life. It is an interesting speculation that the modern philosopher and theologian is somewhat concerned over the reduction of pain in present-day America, resulting from scientific and technologic advances which spare us from much of the physical suffering endured by our forebears. The privations and discomforts of pioneer living have been replaced by the more abundant life of the "fair deal" and the modern medical center; the vigorously and painfully emotional revival camp meeting by the more sedate suburban church.

It is with a more restricted aspect of pain that this essay is concerned—bodily or physical pain.

Analysis of the sensory aspect of pain begins at least as far back as 1800 with Erasmus Darwin.[3] He stated, "Pain results whenever the sensorial motions are stronger than usual." By this we may interpret him to mean that any neutral sensation becomes converted into pain when it becomes sufficiently intense. In this statement he proposes a *mechanism* for pain sensation and thus offers to the experimentalist an opportunity for testing an hypothesis. It was not long thereafter that Charles Bell[4] discovered the function of the dorsal roots of the spinal nerves as that of carrying the sensory messages *to* the central nervous system; the ventral roots of the spinal nerves conducted excitation *away* from the spinal cord to the muscles and other organs. Thus, an animal or man with cut dorsal roots can feel no pain, no matter how intense the stimulus, within the area served by the severed nerves. This recognition of the difference in function of the ventral and dorsal roots of the spinal nerves established for sensation, including pain, a sound anatomic basis and justifies the hope that some day the nature of pain sensation will be understood.

In 1840, another important step toward the understanding of pain sensation and sensation in general was made by Johannes Müeller.[5] He proposed his theory of "specific nerve energies." That is, for each sensation there is a specific environmental energy for which the peripheral sensory ending is especially adapted, and a specific peripheral nervous apparatus for each sensation by which

the brain receives the particular excitation and thus gives rise to the appropriate sensation. No difficulty has been experienced in applying Müeller's theory to vision, hearing, taste, and smell, but in respect to "touch," which includes many sensations such as pressure, temperature, proprioception, and pain, there has been less agreement.

With Donaldson,[6] Goldscheider,[7] and von Frey,[8-10] pain sensation came under the scrutiny of the experimental psychologists, and these were joined by neurophysiologists such as Head[11] and MacKenzie.[12] Since the beginning of the century, psychologists, physiologists, pharmacologists, and physicians have combined efforts in the study of pain sensation with no small success, resulting in large areas of agreement.[13] Thus, evidence supports the ancient view that the feeling states associated with pain may be the most relevant aspect of pain to the sufferer; yet, there is little question but that pain is a sensation with its special structural, functional, and perceptual properties. In this sense, bodily or physical pain (i.e., pain sensation) is but a part, and not necessarily a major part, of a larger experience which might, for simplicity, be called the pain experience. This experience is understood to include not only the sensation of pain but all of the associated sensations, emotional reactions, and affective states as well, the resultant being the pain experience for a particular individual under the particular circumstances at the time. If allowance be made for conditioning, a particularly easy situation where pain sensation is involved, it is seen that many elements of the "experience" can be evoked by any sensation. Thus, we are back to Aristotle's "quale of the soul." It is hoped that this distinction between pain sensation and the pain experience will become clearer in the following paragraphs because this is the key to understanding pain sensation.

METHODS OF STUDY

A quantitative study of sensation begins with the measurement of a stimulus, and with the identification of the conscious dimensions of the sensation through introspection. According to Boring,[14] sensation has four dimensions in consciousness; namely, quality, intensity, duration, and location. For pain, the qualities of pricking, burning, and aching have been identified. Intensity of pain, through the application of the methods of psychophysics, can be estimated quantitatively. Duration and location, vitally important clinically, are well understood and thus need concern us less here. In every instance, it is the verbal report of the subject that marks the end point for pain, whether it be the threshold measurement or change of quality or any other aspect. There does not exist at this time any electrical recording technique or any other "objective index" which can be specifically and reliably correlated with pain perception. It is therefore necessary to make a start on the analysis of pain sense by selecting a suitable stimulus and measuring the pain threshold, that is, the intensity of the stimulus which will evoke barely perceptible pain (threshold pain).

Pain can be evoked by a variety of stimuli, but they can be classified under one of the following types of energy: mechanical, electrical, chemical, and thermal. Each type of stimulus has for test purposes some advantages and some disadvantages. For example, visceral pain is elicited most easily by

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mechanical and chemical stimuli, whereas electrical means are more convenient for direct nerve stimulation. Thermal stimuli are particularly well suited to the study of skin pain, and heat has the added advantage of the association of a large body of experimental data and theoretical exploration on the effects of temperature on tissues and reaction rates of biochemical processes. In studying the various aspects of pain sense, the appropriate stimulus must be selected and adapted for measurement to the particular tissue. In my laboratory, all of the above stimuli have been used, but skin pain has been most thoroughly investigated, and the thermal radiation method has been used for the most part and will be described first. To indicate the close parallelism between pricking and aching pain with respect to intensity, an experiment using a pressure stimulus to evoke aching pain will also be described.

The Thermal Radiation Method.—The arrangement of essential parts of the apparatus for measuring pain threshold by means of thermal radiation is shown in Fig. 1. Modifications of this apparatus designed to increase the ease of operation have been made since its first description in 1940. However, these changes have not altered the essential principles around which the equipment was first designed.

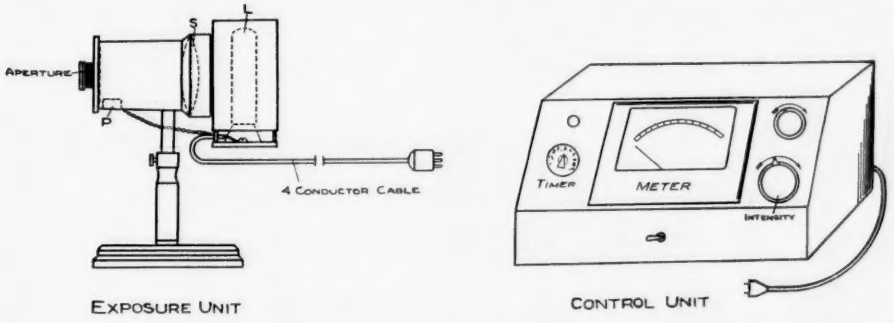

Fig. 1.—The Hardy-Wolff-Goodell Dolorimeter. P = electronically controlled relay for actuating shutter; S = corrugated biconvex lens; L = 500 W. projection lamp.

The surface of skin to be tested was blackened with India ink in order to insure a high degree of absorption of the thermal radiation and to render the experiments independent of the degree of natural pigmentation of the skin and possible effects of subdermal heating from rays which penetrate below the skin's surface. With the India ink-blackened skin, the stimulus could thus be considered purely thermal. The light from the incandescent lamp (L) was focused by the condensing lens (S) through a fixed aperture onto the subject's skin. The aperture, circular in shape, was cut through a heat-insulating material and was 1 to 2 cm. in diameter. In back of the aperture was interposed a shutter which could be opened and closed to regulate accurately the duration of exposure to the stimulus. In most experiments, a three-second exposure was chosen as standard.

It has been discovered that the pain threshold measurements in terms of the number of millicalories (0.001 gram calories) per second per square centimeter (mc./sec./cm.^{2}) of thermal radiation, which is barely able to evoke a mini-

mal pain sensation, depend upon the level of skin temperature just prior to starting the exposure. This relationship is shown in Fig. 2 in a study on three subjects. In this experiment, the skin temperature of the subjects was altered by exposing them in a cold and hot room and making measurements of skin temperature and pain threshold at levels of skin temperature from 18 to 43° C.

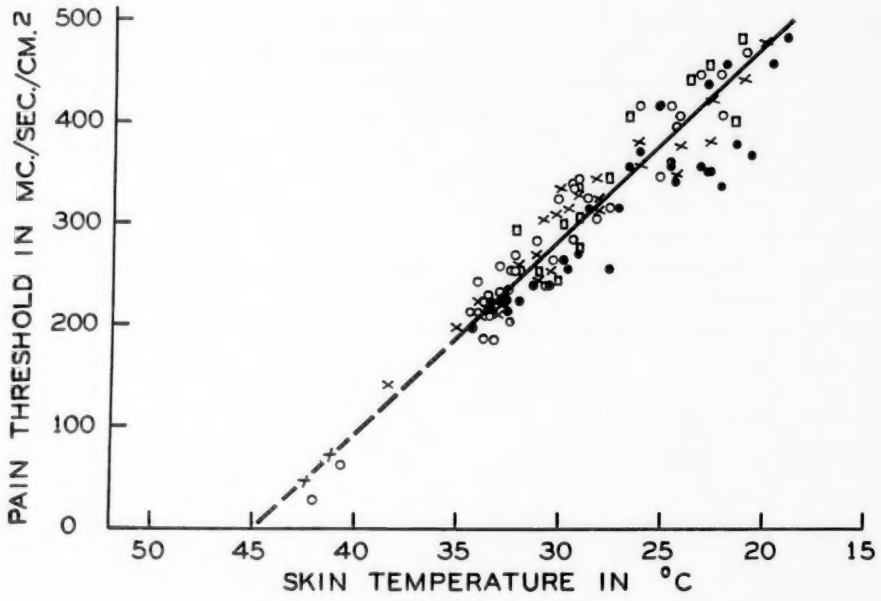

Fig. 2.—Relation of pain threshold to level of skin temperature.

The pain threshold measurement can be corrected for skin temperature by the use of the following formula: $PT = 220 + 20\ (34° C. - T_s)$. In this equation, PT represents pricking pain threshold for skin temperature of 34° C. T_s is the temperature of the skin in degrees centigrade at the time of observation. From the formula, it is seen that a 1° C. change in skin temperature alters the pain threshold by roughly 10 per cent or 20 mc./sec./cm.^{2} Thus, for the precise measurement of pain threshold, the initial skin temperature must be measured, and this can be most easily accomplished by the use of a radiometer. The details for the calibration and adjustment for a dolorimeter have been fully put down in a previous publication[13] and therefore need not be discussed further.

The procedure for measuring the pain threshold is as follows: It is explained to the subject that the procedure is not a test of his ability to *endure* pain, but rather of his capacity to detect the *first trace* of pain. The subject is told to concentrate his attention on the sensation coming just at the end of the three-second exposure. If the subject has not previously been tested, he is first exposed to a stimulus (100 mc./sec./cm.^{2}) which will result in only a mild sensation of warmth. This is followed by a stimulus at the level of about 250 mc./sec./cm.^{2} In nearly every instance the subject will experience a definite pricking pain

during the exposure to this higher intensity. The test is continued by lowering the intensity of the stimulus to about 120 to 150 mc./sec./cm.^{2} for the next exposure. If no pain is reported, the intensity is increased 15 to 20 mc./sec./cm.^{2} and another exposure given on an adjacent skin area. The stimulus is increased in steps, allowing 15 to 20 seconds between exposures of neighboring skin areas, until the subject first reports pain. As noted above, the skin temperature is measured prior to the stimulation each time.

The pain threshold in the normal subject, measured as described above, has a relatively narrow range. Fig. 3 shows results obtained on a group of 150 men and women from hospital wards and laboratories. The ages range from 14 to 70 years, and among the subjects were members of various racial groups normally seen in a New York City hospital.

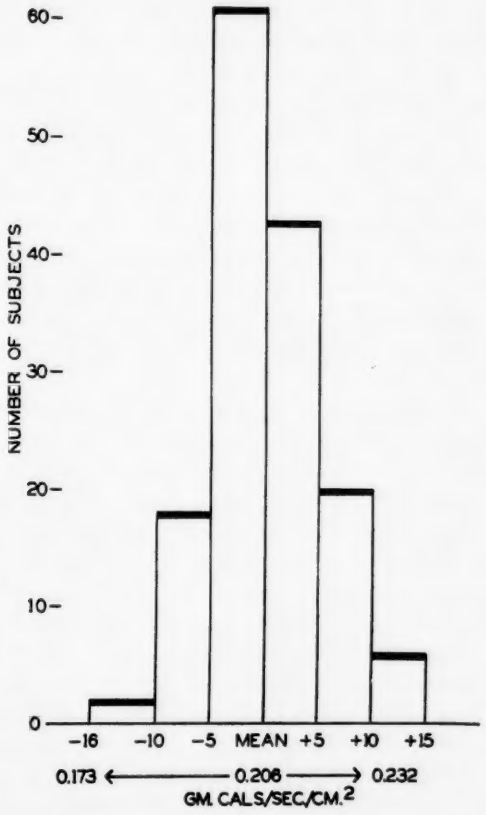

Fig. 3.—Distribution of pain thresholds measured by the thermal radiation method.

There were 324 measurements in this series and the data were considered on the basis of one measurement on each subject, this being the average of the observations made on the particular individual. Each subject was asked to express an opinion about his or her own pain sensitivity. There were wide

variations in the expressions of these personal estimates such as, "I am exquisitely sensitive," "About average," and "I can stand a lot of pain." There was found to be no significant correlation between the personal estimation of hyper- or hyposensitivity and the measured pain threshold.

It has been observed, however, that differences in the *reaction* threshold, determined by wincing or withdrawal of a stimulated part, could be correlated with racial and geographic origin.[15] Thus, despite the uniformity in pain threshold among these racial groups living in the United States, the question was still open as to whether or not subjects who had little contact with Western culture would have pain thresholds in the range reported above. During the summer of 1952, opportunity was afforded to study the Alaskan Indians and Eskimos still living according to their own customs and influenced little by Western culture. During their lifetime, they are regularly exposed to long periods of extreme cold, and experienced observers have noticed that it is possible for these people to work with their bare hands in the cold for appreciably longer periods than can most white people.

The Indian subjects were obtained from the village of Fort Yukon. Twenty-six subjects were studied in the age range from 12 to 78 years, although there was considerable uncertainty about the age in the older subjects. About two-third of the group had had one or more years in the local mission school.

The Eskimo subjects were obtained from the region of the Endicott Mountains of the Brooks Range, where a small village of Eskimos live by hunting and fishing. In this very isolated region, the Eskimos had, at the time of observation, only occasional contact with white men.

For direct comparison, 32 subjects from the Ladd Air Force Base were also measured.

The laboratory conditions under which these measurements were made deserve some comment. The Indian subjects were studied individually in a relatively warm, quiet room, whereas the Eskimos came as a group into an old tent which served as a laboratory. Men, women, and children in arms were present during the tests. The tent was drafty and cold as well as noisy, thus contributing considerably to the distraction of the subjects. Also, communication with the Eskimos was more difficult because none of their group spoke English, and the significance of the test may not have been understood by all. The results of the measurements on these three groups are shown in Fig. 4.

The means os measurement in the three groups are not significantly different, one from the other, and thus it can be concluded that in these groups, cultural differences were not such as to affect the pain threshold measured by the thermal radiation method. The Eskimo subjects tended to have slightly lower thresholds than the whites or the Indians and there was a greater variability in the threshold measurements in this group. It is felt, however, that these differences were probably due to the difficulties in communication with the subjects and the field conditions under which the tests were made. Thus, the ability of the native Alaskan Eskimo and Indian to expose their hands to extreme cold without pain is not associated with an elevation of this threshold.

The uniformity of pain threshold described above must be considered in direct contrast to the everyday experience of the physician who sees in his pa-

tients wide differences in apparent sensitivity to pain. This contradiction, however, is more apparent than real because the pain threshold measurement does not represent the entire reaction of the patient to minimal pain, and it is the over-all reaction of the patient that is observed by the physician. Expressions

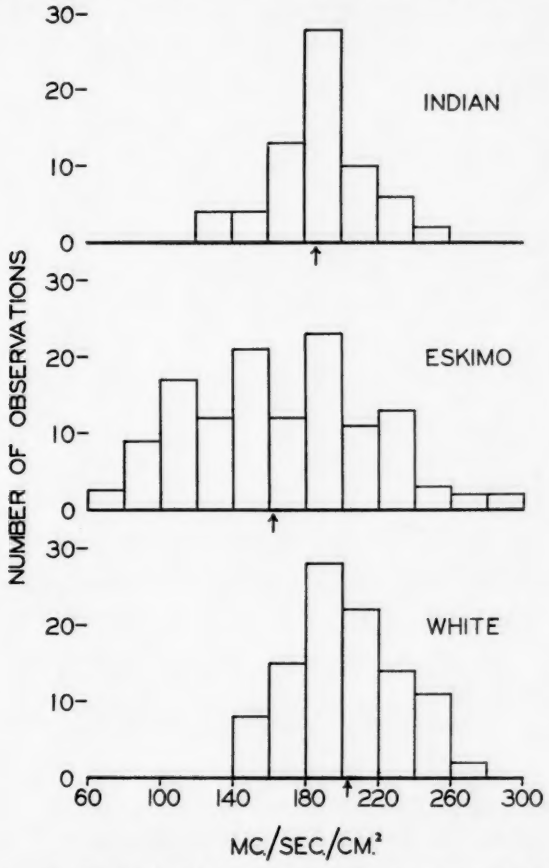

Fig. 4.—Distribution of pain threshold measurements corrected for skin temperature for Indian, Eskimo, and white subjects.

also on the part of the individual such as "I am exquisitely sensitive" indicate a certain degree of insight on the part of the individual into his own reactions to minimal pain or even to the threat of pain, however small. These reactions may represent a conditioning on the part of the individual which will bring about many reactions (normally associated with pain) when presented with an associated nonpainful stimulus. It is largely for this reason that the physician is unable from his observation of a patient to evaluate the intensity of the pain, if any, which the patient is suffering.

NOCICEPTION THRESHOLD AND PAIN THRESHOLD

A glance at Fig. 2 reveals that when the skin temperature is about 45° C., no stimulus is required to evoke pain. Also, the fact that the relationship be-

tween levels of skin temperature and pain threshold is characterized by a straight line suggests that the pain threshold measured in millicalories per second per square centimeter measures the energy which, applied for a fixed time, will raise the skin temperature to 45° C. Thus, it is the skin temperature level which is critical as regards the production of thermal pain in the skin. With the development of a dependable method for measuring skin temperature during exposure

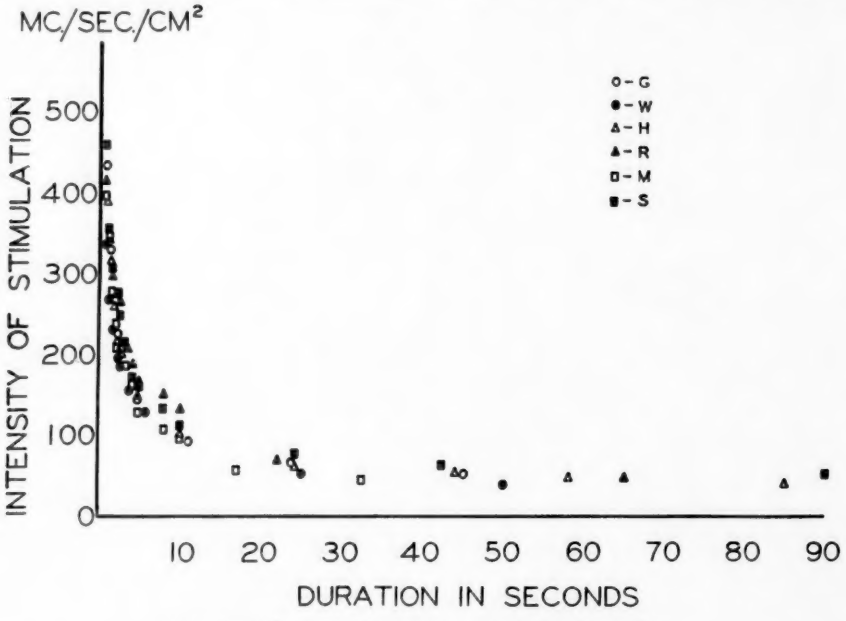

Fig. 5.—Pain threshold measurements in 6 subjects for different times of exposure to thermal radiation.

to intense thermal radiation, it became possible to explore further the relation of skin temperature to pain threshold and to nociceptive responses in man and animals. The experiments to be described were designed to measure the effects of skin temperature and of duration and intensity of a thermal radiation stimulus upon the pain threshold and upon the threshold of the flexor reflex in paraplegic man and reflex responses in the rat and guinea pig. In the pain threshold measurements, 6 subjects were used and measurements were made by exposing blackened skin of the forehead to thermal radiation for lapses of time varying from 0.25 to 300 seconds. The skin temperature was measured prior to irradiation for each study. The results of this test are shown in Fig. 5.

The results formed the usual type of strength duration curve so familiar to the neurophysiologist. The lowest intensity of radiation capable of evoking pain was 40 to 45 mc./sec./cm.², and roughly 90 seconds of exposure were required to evoke pain at this intensity. The more intense the stimulus, the shorter the duration of exposure required, almost in direct proportion. From the equations developed by Buettner,[16] the temperature of the skin reached at the end of an exposure to a known amount of thermal radiation can be computed. If this calculation be made for the results shown in Fig. 5, the average skin

temperature at which pain was felt is 45.7 ± 1.7° C. This result confirms those shown in Fig. 2, obtained by altering the skin temperature and measuring the pain threshold at different skin temperature levels. In the use of the equations developed by Buettner, an assumption has to be made concerning the thermal constants of the skin, and thus it is more satisfactory to make direct measurement of the skin temperature during the radiation exposure and to determine the exact temperature at which the subject reports pain. Using a new type of radiometer which could respond within one-tenth of a second to skin temperature changes, measurements were made of the skin temperature before and during irradiation to various intensities of thermal radiation. The temperature was noted when the subject reported pain. The results of these tests are shown in Fig. 6.

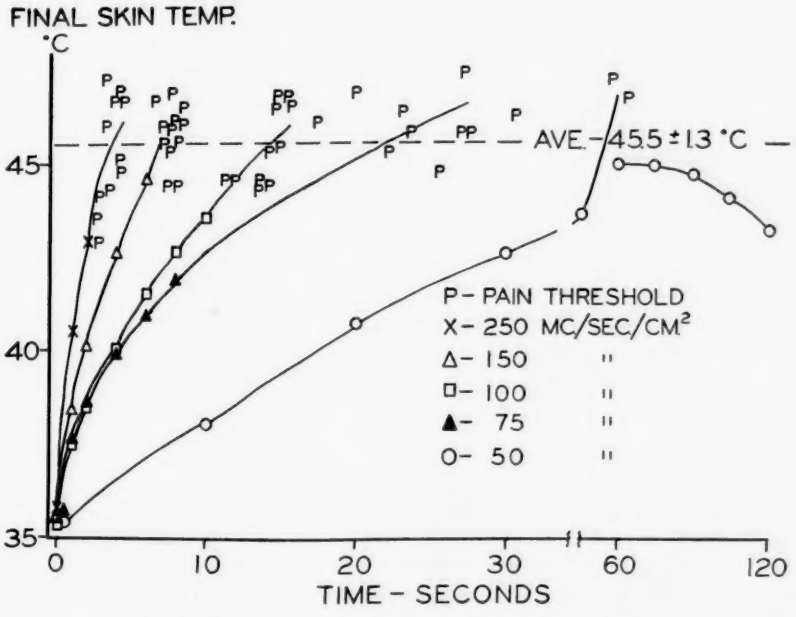

Fig. 6.—Elevation of skin temperature following exposure to thermal radiation. *P* denotes report of pain.

It is seen from the figure that the skin temperature rises more rapidly the more intense the radiation, and that at roughly 45° C., for all intensities studied, the subjects reported pain. For the lowest intensities of radiation, the skin temperature was observed to rise to a level of about 42° C., and thereafter to decrease. This fall in skin temperature was undoubtedly due to increased blood flow in the area. On other occasions, however, the skin temperature, instead of falling, would rise continuously to the pain point, indicating a vasoconstriction in the area. It is not understood at this time what mechanism is involved in bringing about either a vasoconstriction or vasodilitation when the skin is heated to a temperature just below the pain threshold level. It is noted that the reports of pain threshold for all intensities of radiation were at approximately the same level of skin temperature, thus confirming the calculations mentioned above.

The constancy of the temperature of the skin which evokes pain raised the question as to whether or not, at 45° C., a skin temperature might not also be productive of reactions associated with pain as well as of pain itself. To answer this question, the threshold of flexor reflex was measured in a paraplegic subject—a young woman who, fifteen years earlier, had suffered section of the spinal cord at about the tenth thoracic segment. A thorough neurologic examination showed complete volitional paralysis in the lower extremities and anesthesia below the umbilicus.

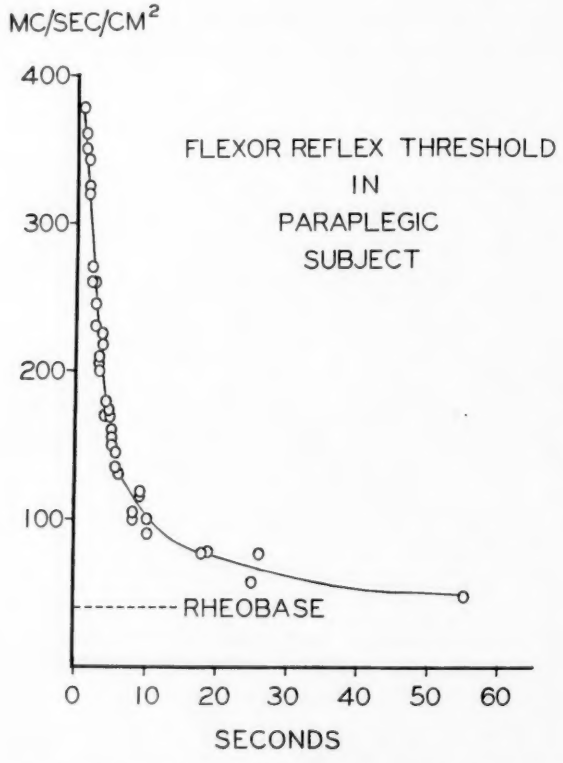

Fig. 7.—Threshold of flexor reflex in paraplegic subject. Rheobase = smallest stimulus capable of evoking reflex during prolonged exposure.

Measurements of radiation intensity, exposure time, and initial skin temperature were made on the dorsum of both feet in tests eliciting the flexor reflex. The pain threshold was measured on the dorsum of the hand and was found to be in the normal range of 204 ± 20 mc./sec./cm.², or, expressed in terms of skin temperature, the pain threshold was 43.6 ± 1.1° C.

In Fig. 7 are plotted the averages of 150 measurements of flexor reflex threshold of various intensities of stimulation and exposure times. A calculation of the skin temperature reached at the instant of evoking the reflex shows that the reflex was elicited when the skin temperature was 44.1 ± 0.75° C., a value

which is statistically indistinguishable from the pain threshold. The striking similarity of the curve in Fig. 7 with the pain threshold plotted in Fig. 5, and the fact that the reflex and pain thresholds are the same, strongly suggests that the pain and reflex are initiated by the same event; i.e., "noxious stimulation." Further, it suggests that noxious stimulation is a phenomenon of broad biologic importance and that its effects should be observable in animals as well as in man. To test this hypothesis, the thresholds of the reflexes of two species, rats and guinea pigs, were measured. The results of the studies on these two species are plotted as averages in Fig. 8.

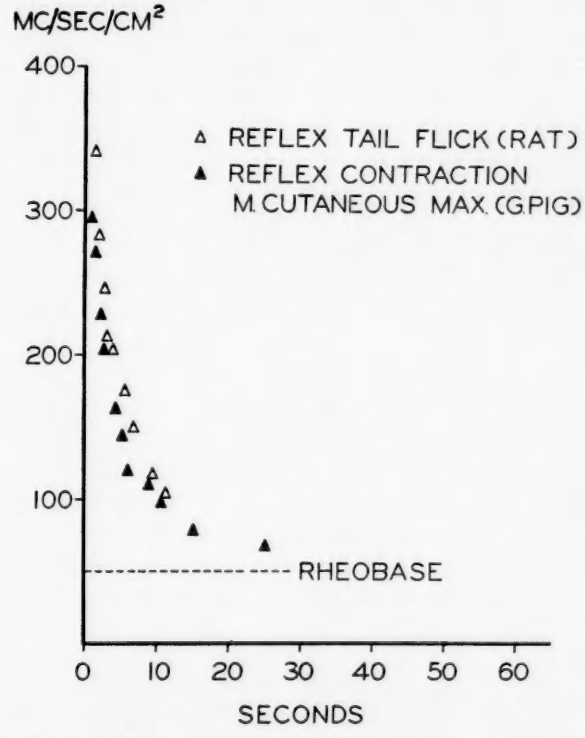

Fig. 8.—Reflex threshold in the rat and guinea pig from thermal stimulation.

The effect of duration of exposure upon the reflex threshold is seen to be essentially the same as that for pain threshold in man. Not only are the curves similar in shape, but they have the same rheobase, i.e., 40 to 45 mc./sec./cm.^{2} Furthermore, a calculation of the temperature of the skin evoking these reflexes shows that the response in the guinea pig was elicited at a temperature of 44.7 ± 0.51° C., irrespective of exposure time, initial skin temperature, or radiation intensity.

The fact that the skin temperature is the one invariant suggests that the temperature of 45° C. is somehow critical for the skin. In a series of experiments on production of skin burns, Moritz and Henriques[17] showed that if the human skin is raised to a temperature of 44° C. and maintained at this temperature for

several hours, transepidermal necrosis will occur. Furthermore, if the skin is raised to a higher temperature, a progressively shorter time is required to produce skin damage. A temperature of 44 to 46° C., however, was the lowest which these authors found capable of producing observable damage in the skin. Thus, the fact that pain is initiated at a temperature of 45° C., the lowest temperature which will produce tissue damage, suggests that there is a strong link between pain and production of tissue damage. Henriques pointed out that the rate of burning of the skin was essentially the same as the rate at which natural proteins are denatured in vitro, and from this he suggested that thermal damage of the skin is the result of the denaturing of vital cellular proteins. This theory has become widely accepted by those studying thermal burns although the details of Henriques' formulation have been somewhat modified. Although the skin temperature of 45° C. appears to be critical for pain, nociception, and tissue damage, one important difference must be noted. Pain and nociception are evoked when the skin reaches 45° C., whereas tissue damage requires that the skin be held at this temperature for many hours. Thus, tissue damage is an integrating process, whereas pain and nociception must be related to the rate of tissue damage rather than to tissue damage itself.

Before discussing further the relationship between pain and tissue damage, it is necessary at this point to introduce the concept of the measurement of pain intensity.

MEASUREMENT OF PAIN INTENSITY

The possibility of measuring the intensity of pain as distinguished from the measurement of pain threshold has been viewed, in the past, with skepticism. However, the concept of measuring the dimensions of other sensations has been accepted and proved most useful. For example, the practical benefits derived from the measurement of brightness, hue, and saturation of colors in respect to the visual sense have been productive of results so important that no one any longer objects, even on theoretical grounds, to the scaling of the dimensions of visual sensation.

Measurement has been broadly defined by Stevens[18] as the process of relating or assigning, according to specific rules, distinctive terms or numerals to objects or events. The fact that relations can be assigned under different specification provides the possibility of different kinds of scales and measurement. Thus the question of measuring the dimensions of a sensation reduces itself to that of devising proper methods.

As regards the measurement of any of the sensory dimensions, the first process involves the linking of a name or number system to the discriminable aspects of the sensation. These, according to Boring, are quality, intensity, duration, and extension. As regards pain, we have mentioned the qualities of pricking, burning, and aching, and the assignment of such terms constitutes a scale descriptive of pain quality. Nominal scales for pain are in general use but, as no clear analysis in terms of sensory dimensions is applied, the description of pain is often confused. For example, "sharp" in reference to pain may mean either narrowly circumscribed, of high intensity, or of short duration. Also, "acute" may mean either narrowly circumscribed, of high intensity, of short dur-

ation, sudden in onset, or prostrating. On the other hand, terms such as "dull" or "lancinating" are somewhat more specific, "dull" always meaning an aching pain of three-dimensional extension, whereas "lancinating" refers to swift change in location without specification as to intensity or quality.

Ordinal scales, using descriptive terms denoting intensity of pain, are in common use. Such words as "mild," "moderate," "severe," and "intense" are used to convey impressions of pain intensity. The term "unbearable" is also used and may designate equally a threshold pain or pain of the highest intensity. Early efforts at devising a scale of pain intensity were made by Wolff[18a] and his collaborators in the early 1930's. These investigators employed the scale of "plus" values in order to provide a closer description than that previously allowed. Wolff's scale of pain intensity in terms of "plus" values, although employing numerals, represented only the *order* of increasing intensity much in the same way as the descriptive terms "mild," "moderate," "severe," and "intense."

The necessary measurement for a pain scale of intensity values is the measurement of *differential thresholds*. This measurement requires determination of the smallest change in stimulus that can be recognized as evoking a change in pain intensity at least 50 per cent of the time. The determination of this just noticeable difference (jnd) reveals the limit of discrimination of the sensory equipment in respect to pain intensity. Such measurements have been in common use in other sensory categories for many years; there are, for example, roughly 570 jnd's[19] for visual brightness between the threshold of vision and the dazzle point, and for warmth sensation there are 90 jnd's between the warmth and pain thresholds.

In the quantification of pain sensation, one begins with the smallest perceivable pain, i.e., threshold pain. It is seen that the threshold pain is a just noticeable difference above no pain at all and is therefore the first jnd. Starting with pain threshold stimulus, the procedure is to increase the stimulus magnitude until the individual barely recognizes an increase in pain intensity—this is the second jnd. Beginning with the pain just greater than the threshold pain, one can further increase the stimulus until the subject again appreciates an increase in pain intensity, thus marking the third jnd. This procedure is repeated systematically until all jnd's above the pain threshold have been tested.

In Fig. 9 is shown a diagram of the experimentally determined jnd's for pain, plotted diagrammatically as small vertical steps, as they are related to various intensities of stimuli above threshold. Thus, as the stimulus is increased above threshold, more jnd's are appreciated until finally, at a stimulus of about 540 mc./sec./cm.^{2}, no further increases in pain are appreciated. The total number of jnd's from zero pain to maximal pain is 22. It is possible, of course, to increase the stimulus far above that which will produce maximal pain, and although the stimulus will increase in its destructive power, it does not evoke pain of any greater intensity than that perceived at the twenty-second jnd. A sensory scale for pain can now be set up, based on the psychophysical data shown in Fig. 9, and for convenience it has been set up on the basis of one dol = two jnd's. To evoke a pain of known intensity, therefore, it is necessary only to

measure the pain threshold and to add to the threshold stimulus an intensity of stimulus large enough to cover the number of desired jnd's. The pain thus induced will be of the desired intensity measured in dols. An important distinction is to be made between intensity of pain and intensity of the stimulus. It is possible to make direct measurements only of the stimulus, and the psychophysical data shown in Fig. 9 are required to show the relationship between sensory intensity and the stimulus intensity.

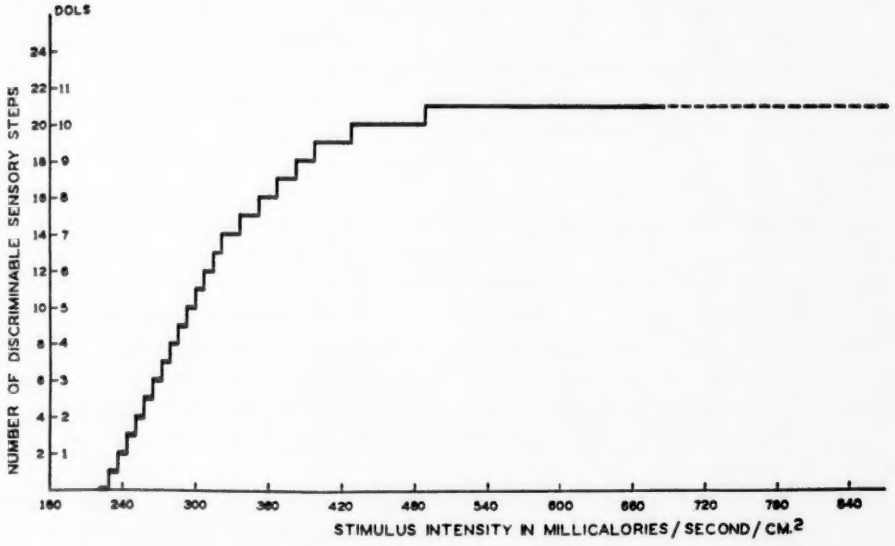

Fig. 9.—Graphic representation of the relationship of the number of just noticeable differences in pain intensity to the intensity of the stimulus.

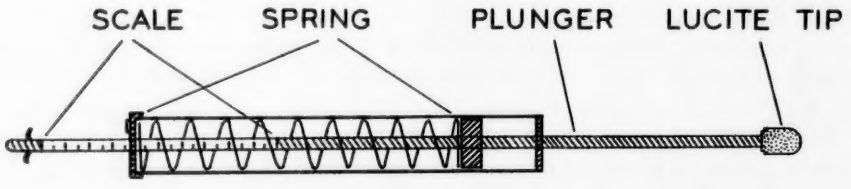

Fig. 10.—Coiled spring esthesiometer—"Algesimeter."

THE PRESSURE METHOD OF EVOKING PAIN

The intensity of aching pain can be measured by a process essentially the same as described above for pricking pain. By far the most common method of inducing aching pain for experimental purposes is that of exerting pressure on subcutaneous tissues.[20,21] A suitable apparatus for stimulating pain from the periosteal tissues of the forehead is shown in Fig. 10.

This apparatus consists of a plunger surrounded by a metal sleeve within which is mounted a steel spring. The force in grams exerted on the tissue by the rounded plastic tip of the plunger 1 cm. in diameter is read from a scale which indicates the degree of compression of the steel spring. Measurements of pain threshold have been made with this instrument on the foreheads of 4 normal subjects by placing the plunger tip upon the head and increasing the pressure until the subject reported pain. The tests were made on each side of the midline, using every effort to direct the plunger perpendicular to the calvarium; during the experiment the subject lay supine on a table. The sensory experience elicited by this mode of stimulation was one of pressure increasing until minimal aching pain was perceived.

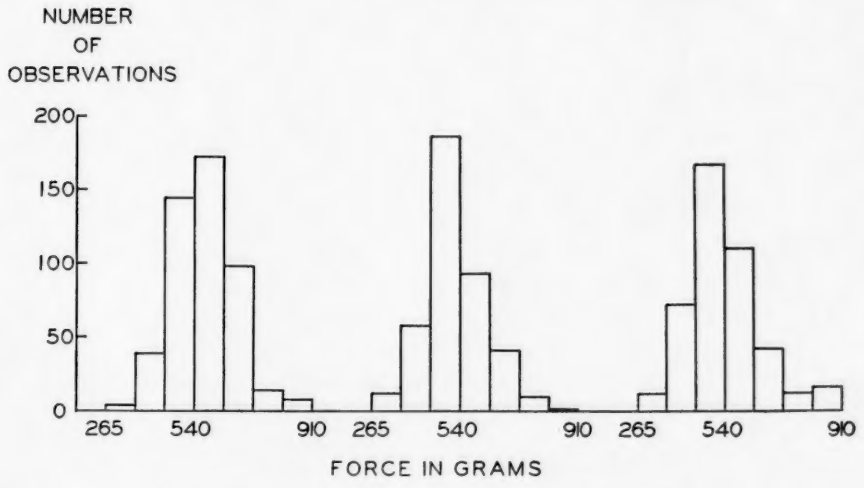

Fig. 11.—Frequency distribution of 800 measurements of aching threshold on the forehead of 3 subjects with the Algesimeter.

In Fig. 11 is shown the results of a large number of measurements made with this instrument. The measurements in Fig. 11 indicate that in terms of physical stimulus the standard deviation of the measurements is quite large; i.e., ±125 Gm., or 25 per cent of the mean threshold stimulus value. However, in terms of the just noticeable difference, this standard deviation is the same as that for the thermal radiation method, i.e., for both modes of stimulation the standard deviation is approximately one jnd. The measurement of intensity of aching pain requires the same type of psychophysical experiment previously described for pricking pain, and the data for the jnd's has been similarly worked out.[22] With these data available, it is then possible to compare the intensity of aching pain with that of pricking pain. The results of more than 250 tests on 4 subjects used in making this comparison are shown in Fig. 12 in terms of just noticeable differences above threshold.

The solid line in the figure represents an expected distribution of reports of pain intensity on the assumption that stimuli, equal number of jnd's above threshold, will evoke pain of the same intensity.

The above experiments show that the intensities of aching and pricking pains can be compared as regards intensities with reproducible results. Also, when such comparisons are made, pains judged as equal are elicited by stimuli which are the same number of jnd's above either threshold. Thus the change in quality of pain itself does not alter the pain-intensity relationship.

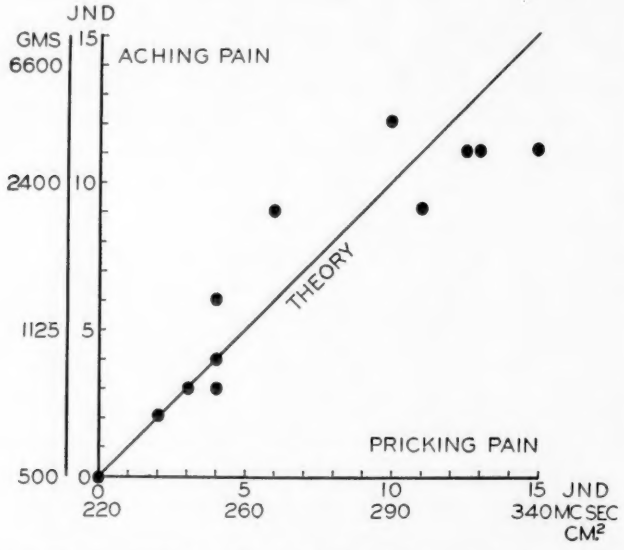

Fig. 12.—Comparison of intensities of aching and pricking pain in terms of the numbers of just noticeable differences above threshold. Stimulus intensities are also shown.

PAIN INTENSITY AND TISSUE INJURY

It has been noted above that a wide variety of stimuli give rise to pain and that pain in this respect is different from other sensations. For example, light and sound are the specific and adequate stimuli for vision and hearing, just as chemical structure is specific for arousing taste and smell. Pain, on the other hand, is completely nonspecific in respect to the physical energies of our environment, except that the stimulus must be more intense than required to evoke other sensations. However, it may be postulated that pain is specific for the processes in operation on the pain fiber ending when pain is stimulated, even though the processes are not specific for the type of stimulation. The preciseness of the pain threshold, whether measured by pressure or heat, supports the idea that some specific kind of stimulation begins at the pain threshold and is not present below it. For convenience, this stimulating effect is called "noxious stimulation" and, as has been seen, it evokes reflex activity at the spinal level and pain in the intact man. It has also been noted that the threshold for noxious stimulation by heat is very near 45° C. for the skin of man, the rat, and the guinea pig, and that at this temperature, burning of the skin begins. It is, of course, possible that it is mere chance that these phenomena begin at the same temperature, but it is so suggestive of an important relationship that it is desirable to

see if any other parallelism exists between noxious stimulation (as indicated by pain) and thermal tissue injury. Having set up the scale of pain intensity, it is possible to ask whether the rate of damaging of the skin by heat in some way parallels the increase in pain intensity (i.e., noxious stimulation). Fortunately, the work of Moritz and Henriques[17] provides the data which show how rapidly the skin is damaged when heated to temperatures above 45° C. Then, using the data from Fig. 9 for the increase in pain intensity above threshold, a comparison can be made between the tissue-damage rate and pain intensity.

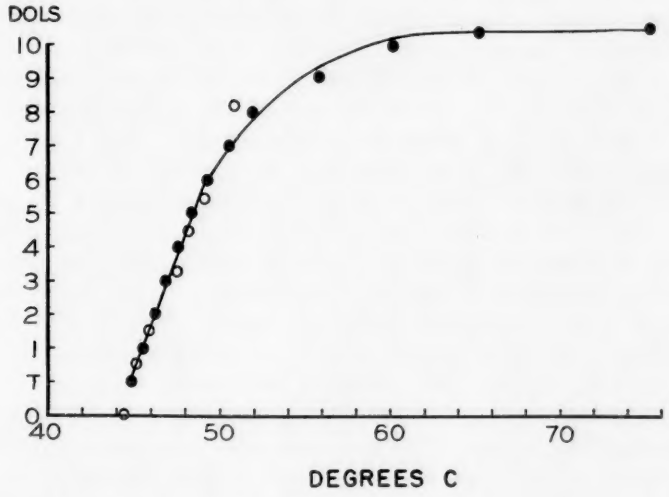

Fig. 13.—Relationship between thermal pain intensity in dols and skin temperature. Solid circles = experimental values; open circles = calculated values; ordinate = pain intensity in dols; abscissa = skin temperatures in °C.; T = pain threshold.

In Fig. 13 is shown a plot of pain intensity as a function of skin temperature (solid circles). Also shown, by the open circles, are the calculated values for pain intensity based on the assumption that the degree of pain depends on the logarithm of the rate of skin damage by heat. It is seen from the figure that over a large part of the pain scale there is reasonably good agreement between the experimental and calculated values of pain intensity at different skin temperatures. Above 8 dols, however, the intensity of pain no longer increases rapidly with skin temperature, and above 67° C. does not increase at all. This may be due to the saturation of the nerve fibers by impulses from the nerve ending, thus limiting the pain intensity. This is similar to the phenomenon pointed out before, to the effect that pain intensity has a definite ceiling or maximum, although the rate of noxious stimulation and tissue damage does not have this limitation. From these experiments the hypothesized relationship between noxious stimulation and tissue damage becomes clearer; namely, (1) both have the same threshold and (2) both depend in a related manner upon skin temperature above the threshold. These two relationships make the close connection between pain, noxious stimulation, and tissue damage seem a good basis for studying physical or bodily pain, and although additional experimentation will be required to

completely establish the theory, there is apparently no other hypothesis presently available which can take into account the known facts. Thus, noxious stimulation is conceived of as the partial denaturing of the cellular proteins of the pain endings by thermal, mechanical, chemical, or electrical energy, thus causing the depolarizing of the pain fiber and giving rise to impulses which are interpreted by the intact nervous system as pain. Accordingly, pain results from noxious stimulation which indicates the beginning of damage to the pain-fiber ending. If the noxious stimulation be maintained sufficiently long, it will result in irreversible damage and death of the tissue. However, thermal pain depends *only* upon the temperature attained by the skin and not upon how long the temperature is maintained, whereas thermal tissue damage depends upon both the skin temperature and the time during which the hyperthermia is maintained. Thus, pain is an indication of the rate at which tissue is being damaged rather than upon the amount or the seriousness of the damage. A rough analogy can be made between pain and the speedometer of an automobile. Pain is analogous to the needle which registers the speed, whereas tissue damage is more analogous to the mileage recorder which indicates how far the machine has gone. In this way, pain is a warning that tissue damage is in progress rather than an indication of potential or existing tissue injury. Thus, extensive wounds may be painless, whereas slight wounds may be extremely painful due to a progressive increase in tissue damage. The latter condition is a familiar one to those who have experienced the intense pain that can arise from a tooth. As an example of the former, Beecher[23] gives data on 215 severely wounded men at an evacuation hospital during World War II. These men were asked to rate their pains to serve as a guide to the giving of proper amounts of analgesics. In spite of extensive peripheral soft tissue injury, penetrating wounds of the head, chest, or abdomen, one-half of these badly wounded men reported "no pain."

It is evident from this that pain is a self-limiting sensation, i.e., high-intensity pain, involving as it must a high level of noxious stimulation, rapidly results in death of the tissue and its associated pain endings. However, a point of importance is the completely reversible nature of these reactions in the early stages. For example, a pain of highest intensity may be evoked for a short time by heating the skin, and there will be no permanent damage to the skin from this treatment. The skin remains intact with perhaps the slightest transient erythema. Lower-intensity pains can be sustained for longer periods with no observable tissue damage.

In Fig. 14 is shown the relationship between thermal tissue damage, pain, skin temperature, and the duration of the skin temperature elevation. For all temperatures and time combinations below the level of the dashed line, no observable tissue damage will be produced by the noxious stimulation. However, as is noted to the left of this figure, pain from threshold to the ceiling pain can be induced without tissue injury. This is the region of completely reversible or subthreshold injury, and here pain serves the purpose of indicating that tissue damage is in progress. Above the dashed line and below the solid line, pain and erythema will occur together but damage is still reversible. Above the solid line, pain is accompanied by irreversible skin damage.

As a consequence of these data, two forces must be considered as playing opposite roles in the relation of pain and tissue damage. The first of these is the role of tissue repair, i.e., those anabolic reactions which serve to maintain the skin in its normally healthy state. The second force is catabolic in nature and is associated with the destructive phases of cellular metabolism. This force, normally balanced by anabolism, increases rapidly at high temperature and can become much stronger than the anabolic reactions. Thus, as skin temperature is increased, the destructive forces due to protein denaturation within the cell increase rapidly until, at 45° C., they are equal to, or just greater than, the anabolic reactions of repair. Above 45° C., the destructive reactions increase at the rate of 300-600 fold for an increase of 10° C. in temperature.[24]

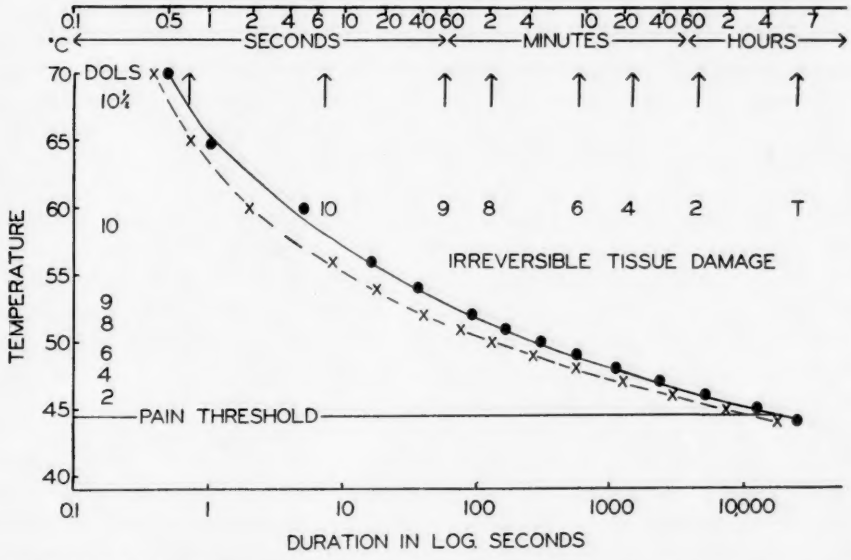

Fig. 14.—Relation of skin temperature, duration of skin temperature elevation, pain intensity, and production of tissue damage. Solid line = threshold for transepidermal necrosis; dashed line = threshold for transient erythema.

This disparity of destruction over repair can have but one effect: the cell will be irreparably damaged and will die. The role of pain in this frame-work is seen to be that of an early-warning system which is triggered when the destructive forces have become equal to the forces of repair. Beyond this point, pain increases progressively, indicating the degree of relative superiority of the damage rates over the repair rates. Pain's usefulness to the organism, however, is limited by the fact that it gives no true indication of either the amount of tissue damage or of the seriousness of the damage. In Fig. 14, the arrows along the upper time axis indicate the times during which the skin can support pain of various intensities before irreversible tissue damage is produced. For example, a 10-dol pain results in skin damage in less than ten seconds. Maximal pain can be sustained for only one second. On the other hand, a threshold pain can be sustained for more than seven hours. An important implication from this is that high-intensity intractable pain is a physiologic impossibility, and no pain,

even at threshold level, can be sustained without remission for long periods of time. So-called intractable pain must therefore be either of low intensity, periodic, or must not be truly pain at all, but rather a combination of nonpainful sensations which are interpreted by the individual as unpleasant and unacceptable.

REACTIONS TO NOXIOUS STIMULATION

In the preceding sections, attention has been focused upon the report of pain by individuals who were intent upon making discriminations in respect to intensity, quality, duration, and extension of the sensation. In such individuals the predictability of pain sensation as regards its threshold has been expressed quantitatively. The close relationship between intensity of pain sensation and intensity of stimulus applied was demonstrated, and the relation of noxious stimulation to the rate of tissue damage was pointed out. Yet, despite the predictability of these features in the especially alerted individual, precise relationships between suffering and the intensity of noxious stimulation are not immediately apparent in the patient. Thus, many suffering individuals seem at first glance to have a variable rather than a uniform sensitivity to noxious stimulation, i.e., to have "pain" modifiable by factors which do not influence the pain threshold in normal subjects. So striking is this apparent contradiction between the observations of "pain" in the subject trained in the analysis of the sensation and in the patient enduring the pain associated with disease or injury, that some observers have preferred to term the latter pain "pathologic" as distinguished from "experimental" pain.[25,26] However, this contradiction is resolved in the realization that for the trained subject the pain sensation can be isolated as an entity to be focused upon for special analysis. On the other hand, the "pain experience" of the patient is a complex phenomenon involving such a variety of features that concentration on the actual pain sensation is more difficult. Pain sensation is but a part of the total pain "experience" and, indeed, may not even be a major feature. To analyze such an experience and to evaluate the contribution of pain sensation, it is desirable to define the *pain experience* broadly as those combinations of reactions involving consciousness which have been observed to be highly correlated with noxious stimulation and pain. Pain sensation is thus the special response to noxious stimuli identifiable by the report of pain by the individual. Some responses to noxious stimulation, although themselves of a reflex nature and not dependent upon consciousness, may give rise to pain and associated sensations either by augmenting the noxious stimulation or by establishing additional sources of noxious stimulation. So important is the relation of these reactions to the phenomenology of pain that they must be given special attention.

Noxious stimulations refer to the particular activity at the nerve endings subserving pain sensation which gives rise to a corresponding sensation of pain and observable reflex activity. In addition to pain, there are other responses to noxious stimulation. These include local tissue reactions at the site of stimulation, neural, muscular, and glandular activity, and the establishment of states of hyperexcitability within the central nervous system at segmental and suprasegmental levels sometimes exhibited as hyperalgesia. Many of these reactions (reflex muscular contractions and establishment of hyperexcitable states) to

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noxious stimulation have been shown to have the same threshold as does pain sensation. However, there is a fundamental difference between pain sensation and other reactions to noxious stimulation; namely, pain intensity is not generally increased by the *summation* of neural impulses from noxious stimulation at different sites, whereas the magnitude of many reactions to noxious stimulation is thus increased. This suggests that such summation in the case of reactions is biologically useful in facilitating mobilization for adaptation and protection, whereas the lack of it for pain sensation prevents overwhelming of the individual by unbearable pain resulting from a summation of effects of multiple noxious stimulation of low intensity.

Prolonged noxious stimulation of the viscera, although not painful in itself, may induce skeletal muscle contraction and thus provide a further source of noxious stimulation and pain. Pain so experienced may long outlast and be anatomically remote from the site of original noxious stimulation.[27] In such instances, procaine infiltration into a muscle may relieve the contraction and thus, interrupting the pain mechanism, may abolish the pain.

Important among the reactions to prolonged noxious stimulation are those which result in the establishment of hyperexcitability within the central nervous system. Such states, maintained by the constant flow of impulses from low-intensity noxious stimulation, make possible the intensification of pain from stimulation of other body regions (secondary hyperalgesia) or from the same locality (phantom limb, intractable pain).[28-30] Due possibly to such summative effects, the reactions to noxious stimulation may be the source of far more suffering than is pain from the original site of noxious stimulation.

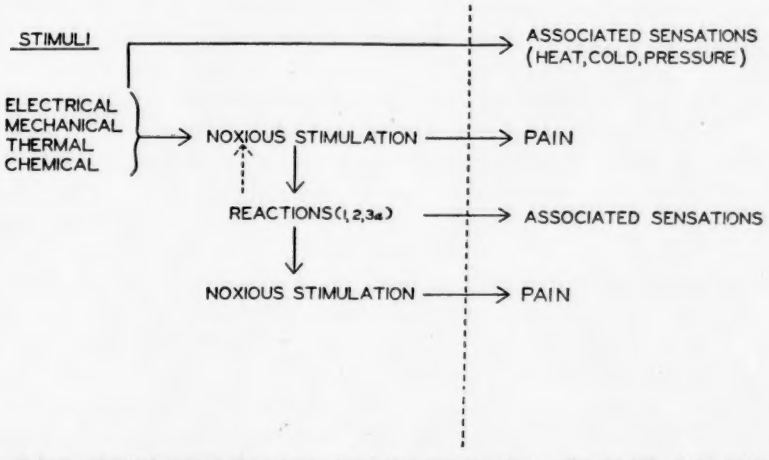

Fig. 15.—Scheme of relationships of noxious stimulation and reactions. To the left of the dotted line, reactions independent of consciousness; to the right of the dotted line, responses involving consciousness.

A diagram indicating patterns of interplay of reactions to noxious stimulation may serve to clarify the complex. Thus, the chain of events is initiated by the original noxious stimulus. This stimulation evokes pain directly, together with associated sensations such as heat, cold, pressure, nausea, etc., and in addition gives rise to a host of *reactions* such as are indicated in Fig. 15, to the

left of the dotted line. These reactions can serve to intensify the effects of noxious stimulation by producing states of central hyperexcitability (secondary hyperalgesia), or by giving rise directly to additional noxious stimulation (primary hyperalgesia). Also, these reactions may result in additional sources of noxious stimulation and pain through intense reflex activity, i.e., smooth and skeletal muscle contraction, vasomotor, and glandular effects. The sequence of relationships is indicated in Fig. 15 by arrows, and, for convenience, there is shown only one cycle of reaction to noxious stimulation. Many are known to exist. From an examination of the physiologic data available,[13] the importance to the pain experience of multiple reflex reactions is indicated. However, the complete pattern of the reaction relationship requires further exploration in terms of the reactions to pain per se.

REACTIONS TO PAIN

Distinguished from the reactions to noxious stimulation locally, at the segmental and suprasegmental levels, including both consciousness and partly conscious reactions, are those associated with pain itself. These latter presuppose the existence of pain, whereas many of the former can be elicited even in the anesthetized animal or in unconscious man. The distinction between the two response patterns appears to be justified on the basis of the greater complexity and lesser predictability of reactions to pain as compared to the reactions to noxious stimulation. However, the patterns of reflexes elicited by noxious stimulation and the acquired reaction patterns to pain have many features in common, and it is frequently difficult to distinguish one from the other.

Man reacts not only to actual noxious stimulation, as do all living forms, but, having the highest integrative equipment, he is particularly sensitive to threats and symbols of danger. These call forth reactions very similar to those elicited by a painful episode itself. Depending upon the rapidity and magnitude of the adjustments, these reactions may be so intense as to induce pain sensation. Pricking sensations in the face and scalp associated with sudden fearful situations, and the painful abdominal cramps elicited in similar circumstances are well-known examples. Since the adaptive protective reaction, elicited by either noxious stimulation or pain or symbols of danger, may long outlive the precipitating episodes, such reactions may be far more injurious to the individual than the primary tissue damage. Also, and most important, man is a group creature with a long period of development and dependence. He is dependent for his existence upon the aid, support, and encouragement of other men. He lives his life so much in contact with men and with so much concern for their expectations of him that he is jeopardized as well as supported by his fellows, and as a result he may feel threatened more by cultural and individual human pressures than by potentially painful environmental forces. Consider, for example, the general lack of concern for the danger of motor traffic. Hence, the culture in which a man finds himself becomes the major conditioning influence in the formation of individual reaction patterns of pain. Although, until now, these relationships have not been thoroughly explored, it is generally realized that a knowledge of group attitudes toward pain is essential in under-

standing the individual's reaction. A classic example is presented by the Spartans of ancient Greece in their denial of pain, even in the most desperate situations.

In addition to culture conditioning pain reactions, the meaning of pain to the individual may be affected by a number of factors such as hypnosis, suggestion, analgesic agents, or brain injury. Further, since the cerebral cortex is the organ of integration involved in sensation, damage or chemical agents which depress cerebral function may not only modify the effects of noxious stimulation but also alter the attitude toward pain. Thus, following a treatment by a trusted physician, even the most intense noxious stimulation may arouse no visible reaction, whereas the mildest noxious stimulation because of some symbolic significance of danger may evoke protective and adaptive reactions of major proportions.

The experience of pain in an individual, regardless of how induced, self-inflicted, accidental, or occurring from disease, brings with it highly developed responses in certain cultures by which the individual is "protected" or "cared for." The individual who cannot express his need to be cared for when free of pain because of cultural demands of self-reliance, initiative, and independence, finds himself in a socially or culturally acceptable position when he is experiencing pain. Thus, being "disabled" allows of, or even puts a value upon, being dependent and willing to be cared for. Indeed, he may be disapproved of if he is impassive, uncooperative, or a "poor patient." Under such circumstances, the ideal behavior becomes one of almost complete passivity in which the individual remains immobile, allows himself to be fed, turned, and bathed. His creative work and occupational satisfactions are denied him. He is allowed no decisions and may assume no responsibilities. Such a pattern has been rationalized as an attempt on the part of culture to remove all burdens from the "sick," and thus promote recovery.

Pain experienced in certain parts of the body is culturally more acceptable and brings with it greater sympathetic response than pain from other parts. Pains from the genitalia, rectum, and anus, or pain resulting from a fall on the buttocks, do not evoke the sympathetic response that pains do from the head, extremities, chest, or even from the abdomen. Hence, pains of minor intensity from certain regions of the body are complained of more than others, and may therefore be more conspicuous when pain has been incorporated into a way of life.

The hypo- and hyperdynamic nature of many of the reactions of pain are noted as contributing to processes of adaptation and re-establishment of homeostasis.[31] Pain is an important factor in conditioning behavior in forming sex patterns, and may shape religious rites. Also, individual and cultural attitudes toward pain may constitute the dominant component of suffering in those with disease (pathologic pain). From these data and those in the preceding sections, it is possible to outline in more detail the components of the pain experience and their interrelationships (Fig. 16).

In the figure, noxious stimulation is shown as evoking two major reaction groups: those not dependent upon consciousness, i.e., nociception; and reactions

involving consciousness, i.e., the pain experience. Many of the subdivisions of this outline have been the topics of experimental investigation, and the details of some of the experiments have been presented. At first glance, it might seem as if the functions listed represent all physiologic and mental life. However, the integration of the effects of noxious stimulation can be related in a definite

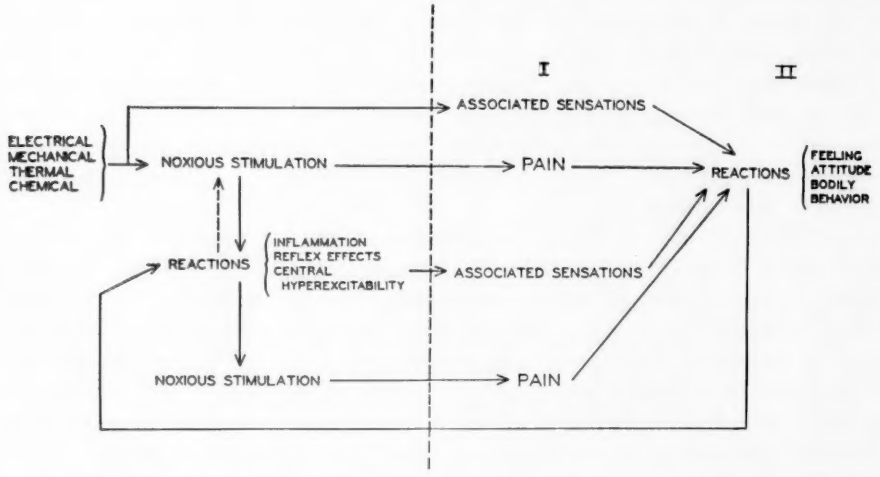

Fig. 16.—Interplay of responses to noxious stimulation not dependent upon consciousness and reactions involving consciousness as affecting the pain. To the left of the dotted line responses are not dependent upon consciousness; to the right of the dotted line, reactions involve consciousness.

pattern to the pain experience already presented. Diagrammatically, the effects can be represented by arrows to indicate the direction of action. This presentation has practical as well as theoretical value since it indicates methods for the control of suffering as well as the pattern of responses involved in the pain experience. Such a concept is especially useful in the understanding of the action of analgesic agents, as a relatively small portion of such action involves suppression of pain sensation itself.

THE EFFECT OF ANALGESIC AGENTS UPON PAIN

Although chemical agents have been used to relieve suffering for many hundreds of years, it is only within the recent past that quantitative methods for study of pain have become available, thus making possible a more precise, systematic study of the effects of such agents in man.

An analgesic may be defined as a substance which, through its action upon the nervous system, serves to reduce or abolish suffering from pain without producing unconsciousness. When a person experiencing pain is given an analgesic agent whose action affects some part of the neural apparatus, there are at least eight aspects of this effect which are factors in the evaluation of its usefulness.

The first aspect is the pain-threshold-raising property of the analgesic agent. In the assay of this property, one can be reasonably precise, but it may not be the most important aspect of the therapeutic effect.

The second is the pain-reducing property of the agent, likewise susceptible to measurement. Although this effect is often related to the pain-threshold-raising property of the agent, it can change independently of the pain threshold.

A third effect is the property of the agent in curbing the influence of noxious stimulation either by direct action upon afferent nerves or upon central excitatory states at the segmental level. Painful contractions of smooth and skeletal muscles are sometimes effectively eliminated by the direct action of procaine upon afferent fibers, or by the more central action of morphine. The sometimes massive, summated responses to noxious stimulation can be reduced or abolished by analgesics.[32]

The fourth feature may be referred to as the capacity of the substance to change the attitude or mood of the subject in pain. Useful therapeutic effects in this category might be promotion of freedom from anxiety, mild euphoria or feelings of well-being, or apathy. As commented upon above, central excitation heightened by the effects of adverse life events, with accompanying feelings such as fear and anxiety, may further augment the intensity of pain. Consequently, reducing or abolishing such states may afford an important degree of relief from pain. Less desirable, however, and even dangerous, would be the stimulation of feelings of extreme excitement, depression, or hopelessness.

The fifth facet may be considered the agent's effect as a sedative and soporific, i.e., whether it induces relaxation and sleep, thus bringing about a state of "rest."

The sixth aspect is the evoking of so-called "side effects," chiefly of an untoward nature, i.e., whether it induces nausea, vomiting, diarrhea, or constipation and other nonpainful but disturbing bodily changes.

Although the aspects of analgesic action just mentioned are conspicuous, there are other important ones such as tolerance, specific sensitivity, absorption into skin or gastrointestinal tract, rate of elimination, etc.[33]

Finally, and eighth, though perhaps not justifiably in a separate category, is the agent's total effect on the person experiencing pain. That is, does the individual "feel better" as a result of its administration? Is this state of better feeling purchased at too great a price in terms of the untoward side effects, and does it add to the general effectiveness of the therapeutic regimen prescribed for the patient?

Since many persons, miserable and frightened, "feel better" because of the symbolic significance of a pill, capsule, or injection, regardless of pharmacodynamic action or lack of it (placebos), the total effectiveness of an agent must be more than the sum of the separate effects listed above. Also, many severely injured persons do not experience so much pain as the damage to their bodies, and perhaps even lethal injuries, might suggest.[23] Hence, a relatively weak analgesic may suffice to achieve "relief" in such cases.[26]

The sensation of pain can be affected by agents acting upon various parts of the physiologic system involved in pain. These include the pain receptors and surrounding tissues, the conducting pathways (including the fiber tracts and the synaptic connections), the internuncial connections in the cord, and the afferent relay nuclei in the thalamus and the cortex.[34] Agents which cause a reduction of pain by action upon the tissues surrounding the pain receptors are not generally considered to be analgesics. For example, ergot, which is

effective in reducing the pain of migraine headache by its vasoconstrictor action, is not classified as an analgesic.[35] In the same category are milk and alkalizing agents, which abolish the pains of peptic ulcer, and atropine and calcium, which relax painfully contracted smooth muscle.

Many of the most useful and desirable effects of analgesics for controlling an acute episode of pain are such as to make many of the agents unsuited, and even dangerous, for general, prolonged use. Among such effects are suppression of reflexes, alteration in attitude, and reduction of sensation.

Pain arises from noxious stimulation, which itself is a product of tissue injury. Thus, procedures which can limit or reverse the underlying processes of noxious stimulation are obviously the most desirable from the point of view of pain relief. The problem, then, is how, in the presence of continued noxious stimulation, pain can best be reduced or abolished. It is likely that the problem will continue to be a perplexing one, but on the basis of existing information, some partial answers can be made.

Pain of long duration is of necessity always one of low intensity, since the rate of tissue injury required to produce noxious stimulation intense enough to evoke a severe pain, 5 to 8 dols, will probably destroy the pain fibers and surrounding tissues so rapidly as to cause a reduction in pain. It is for this reason, perhaps, that in chronic diseases associated with pain, painful episodes alternate with pain-free periods of relatively long duration, and even low-intensity pains are variably present. Constant noxious stimulation of the skin at the pain threshold level will, in the course of several hours, cause hyperemia and complete epidermal necrosis.[36] On the other hand, continued noxious stimulation evoking a 5-dol pain will produce necrosis in fifteen to twenty minutes. Thus, it is clear that high-intensity pains must be of short duration, a matter of minutes at most, whereas pain of low intensity can be supported by the tissues for hours or, with nonpainful periods interspersed, indefinitely.

Pain of low intensity, for which the rates of tissue injury and repair are compatible with tissue integrity (threshold to 2 dols), can fortunately be controlled by the analgesics of mildest action, such as the coal tar derivatives, by placebos, or by distraction, especially during daylight hours. Only 10 to 20 per cent pain-threshold-raising action is required to reduce such low-intensity pain below threshold.

Pain of moderate intensity (3 to 5 dols) and short duration can be eliminated by the opiates. It is important that such pain be quickly abolished in order that the powerful reaction patterns to pain do not become established and in themselves become effective sources of further noxious stimulation and pain.

Pain of high intensity necessitates for its control the elimination of the noxious stimulation or complete unconsciousness. For example, in childbirth, certain analgesics effectively reduce the noxious stimulation of labor, but, for the pain accompanying major operative procedures, an anesthetic, either general or local, is required. Again, the necessity of abolishing such pain is of paramount importance to avoid the reaction to noxious stimulation and pain.

In short, the analgesics are optimally useful in the management of painful episodes of relatively short duration, and in promoting "rest," a state in which the reparative and restorative forces are fostered and exceed those of destruction.

To the extent that an analgesic, through any or all of the aspects listed above, succeeds in inducing rest, its use is appropriate. Inversely, when used in any other manner, it jeopardizes the patient's well-being.

It has been in connection with studies of analgesic action that the terms "pathologic" and "experimental" pain first were used[37] to denote, respectively, the suffering associated with disease and the pain induced for experimental purposes. Whether these two aspects of the pain experience deserve separate categories depends upon the usefulness of the concepts of "experimental" and "pathologic" as applied to pain. As has been indicated, pain sensation is only one of the products of noxious stimulation, and its probable connection with pathologic processes has been indicated as being a sensory index of the rate of damaging tissue. In this sense, all sensory pain is pathologic, whether it be experienced in the laboratory or in the clinic. Further, it has been noted that the physician is generally much more concerned with the *reactions* to noxious stimulation and pain on the part of the patient than with the pain sensation itself. These reactions occur in the laboratory as well as in the sick room and can be made the subject of study in both locations. "Pathologic" pain thus differs from "experimental" pain principally in the degree to which reactions play the more important role in the particular pain experience. The terms "pathologic" and "experimental" do not seem to be descriptive of the really important differences between the suffering of an acutely ill patient and the pain experienced as the result of a laboratory test. If terms are needed to describe the patient's suffering, perhaps a closer study of the patient can reveal information upon which to base a description of the extent to which pain sensations and reactions contribute to the particular presentation made by the postoperative patient, the woman in labor, the chronic sufferer from migraine, the man with low-back pain, or the battle casualty. Surely no single phrase can do much better with the holistic view of human suffering than Aristotle's "quale of the soul." If a deeper penetration is wanted, the clinic must become a laboratory and the tools available to us must be applied rigorously, with care and understanding. Thus, whereas it is important to know that a mild analgesic will successfully relieve the suffering of a postoperative patient,[38] it is even more important to inquire how and why. For example, in some studies of the pain-relieving action of various analgesics in patients, it has not been determined that the patients were even suffering from sensations of pain. Gains in the knowledge of the mode of action of analgesics lie in the direction of making measurements of pain threshold, pain intensity, and of other reactions to noxious stimulation and to pain.

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SUMMARY

1. An historical review of the concepts of pain and its importance as a moral force has been presented. "Physical" pain and "mental" pain have been described in terms of reactions to noxious stimulation and reactions to pain, which together constitute the pain experience of a particular individual under a particular set of circumstances.

2. Uniformity in pain threshold, measured by the thermal radiation method, has been observed in subjects differing in sex, age, race, and cultural background.

3. The thermal pain threshold is reached at a skin temperature of 45 ± 1.7° C., and at this skin temperature, reflexes are stimulated in man and animals (nociception). This temperature is also the threshold temperature for burning the skin.

4. The close connection between thermal pain and tissue damage due to heat was pointed out. Noxious stimulation which gives rise to pain and nociception, having the same threshold and increasing with the rate of tissue injury, is thought to depend upon the excess of destructive over reparative reactions at the pain-fiber ending.

5. Reactions to noxious stimulation and to pain have been discussed in relation to "experimental" and "pathologic" pain and the mode of action of analgesic agents.

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PROBLEMS OF EXPERIMENTAL ALGESIMETRY

And a Comment on the Tooth Pulp Method

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IT IS easy to gain the impression that there are three different methods of experimental algesimetry. One might be designated "animal," another "human" (i.e., healthy normal), and the third "clinical" (i.e., sick patient). Each has its place in the recognition, development, and evaluation of new, more useful analgesic drugs. Each has its advantages and disadvantages. All may (and sometimes do) participate in determining the probable clinical merit of the drugs tested. Common to all methods is some degree of quantitative evaluation of the change in relationship of response to stimulus before and after administration of the drugs being investigated. In animal and human laboratory studies, usually the stimulus intensity or duration is varied to elicit a uniform degree of response. In clinical algesimetry, either the dose of analgesic drugs necessary to obtund clinically occurring pain, or the incidence of relief after certain doses is determined. Relatively recently recognition of the influence of suggestion, both on subject and investigator, has resulted in the evaluation of disciplines to control this prejudicial element. Consequently, placebo medication and the "double blind" regimen have become almost standard.

In facing the problem of evaluation of an analgesic by some algesimetric method, or studying the mechanisms of analgesia, it is useful to know what can be accomplished by the several methods available. For convenience, these have been summarized below.

LABORATORY ALGESIMETRY IN ANIMALS

General Considerations.—The advantages of this approach are: (1) the method is usually relatively inexpensive and permits rapid accumulation of results suitable for statistical examination, (2) the histories of the animals in a particular sample can be much more alike than is possible in a human sample, (3) the nature of response to stimulation (response or no response, time to response or intensity of stimulus) permits relatively inexperienced observers to obtain data, (4) concealment of drug identity is convenient ("blind testing"), and (5) it is practical to "screen" potential analgesic compounds before they are found safe for human use.

As with any technique, there are disadvantages. For example, it is assumed that the response in animals is truly correlated with "pain," but there is evidence that some of the responses employed are spinal reflexes.[1,2] When conscious animals are used more than once, they may become conditioned; hence appropriate controls in technique of stimulus application and in sequence of agent administration are necessary. When stimulating the tooth pulps of dogs, we have found it necessary to stimulate each of two teeth in each of two dogs to detect "sham" responses. A Latin square design helps to correct for training effects. In addition, the fate and action of chemicals may vary between species. Thus, a compound which appears analgesic in animals may not be so in humans.

Finally, relief of pain is a complex involving one, some, or all of the following: blocking of local (peripheral) excitation by the stimulus, or relief of the cause (inflammation); interruption of conduction over the afferent nervous pathway, and modification of perception or interpretation at the level of consciousness. Thus, many mechanisms may be involved. Therefore, although animal studies may reveal potential analgesic action, human studies are necessary for confirmation, if only because the subjects can answer questions.

The Stimulus.—In the use of artificial (electrical, thermal, pressure) stimuli, the intensity, frequency, and duration can be measured, controlled, applied, and reproduced with precision. (This is true of human laboratory procedures too.) In addition, biologically occurring circumstances which produce pain (trauma, distention, infection) may be created in animals more readily than in man, although uniformity of such stimuli is not so good as with "mechanical" stimuli.

Certain drawbacks are evident, too, however. Conceivably, the stimulus may elicit a different chain of events in animals than in man, and the frequency and duration of stimuli optimal for algesimetry may vary between species.

The Site of Stimulation.—Once again, one can contrast advantages with disadvantages. In animals, almost any group of cells may be stimulated, by any method desirable, and the sites marked (dye or tattoo) for precision of restimulation.

On the negative side, one can cite the following: (1) Local reaction to stimulation may vary between species. Histamine release may be involved,[3,4] and the elaboration and/or response to histamine may vary between species. (2) Adaptation of a stimulus site may occur quickly or gradually. Scarring, exfoliation, or thickening of the skin may result from repeated exposure to heat. Nerves may slowly regress in the tooth pulp from enduring or frequent, excessive stimulation. Hyperemia, ischemia, or perspiration can be prompt responses to thermal stimulation. Should these occur without the investigator's awareness, misleading results may be obtained. If sweat were to accumulate between skin and lampblack during thermal stimuli, its insulating properties might cause the threshold of pain to appear elevated by increasing the stimulus necessary to elicit the end point. Hyperemic skin is known to be hypersensitive to heat. (These disadvantages apply equally to human studies.) (3) Some sites (skin) are susceptible to modification by external environmental changes. Some investigators[5] recognize this and conduct their experiments in as nearly uniform an atmosphere as is practical to obtain.

The Response to Stimulation.—Qualitative animal responses such as a squeak, avoidance behavior or a reflex twitch, or quantitative changes like blood pressure measurements, are easily observed and recorded without bias. In addition, certain quantitative evaluations are possible in animal studies that are not practical on humans, such as: (1) recording of sensory impulses over the afferent pathway and in the higher sensorium by microelectrode techniques[6]; (2) direct evaluation of neural or ganglionic blocking power by placing agents directly on the structures; and (3) quantitative comparison of ingested quantities of analgesic agents by properly conditioned animals "suffering" pain.[7]

LABORATORY ALGESIMETRY IN HUMANS

There are obvious advantages in working with humans rather than animals: The subject can report and describe his pain. Atypical circumstances such as coincident distress or bizarre sensations during experiments can be reported and considered; and the fate and action of the drug is comparable to the ultimate goal of algesimetry, human efficacy.

Certain comparisons may be made of laboratory and clinical algesimetry. In laboratory algesimetry, the subject usually has no fear of the procedure, the pain, or his fate, nor any special desire to derive analgesia from medication. It must also be remembered that compounds which relieve clinical pain, but not by elevation of the pain threshold, will not appear to be analgesic in laboratory methods presently employed. (Atropine will relieve ulcer pain but not by its analgesic action.)

There are distinct disadvantages in working with humans in the laboratory: Susceptibility of humans to distraction, diversion, and distortion of the truth is almost certainly greater than in animals. More elaborate controls are therefore necessary. Control of humans *between* experiments is also far less satisfactory than with animals (diet, sleep, etc.). Certain of the animal procedures are impossible in humans and constitute, therefore, possible disadvantages of human algesimetry. Under experimental conditions, the stimulus is artificial, hence different from that encountered in clinical pain. Finally, the subjects are ambulatory and may be more influenced by nauseant, emetic, or sedative effects of a drug.

CLINICAL ALGESIMETRY

On the credit side, perhaps most important is the fact that almost any effort in algesimetry has as its goal, relief of clinically occurring pain. Thus, clinical algesimetry is the ultimate test of analgesics. Obviously, the conditions available for study are representative of the true problems of the clinician who must treat pain. Subjects are abundantly available, and large samples of certain clinical entities afford some homogeneity in an experimental group.

On the debit side, the stimuli are not uniform, measurable, or reproducible, and the sites and areas of stimuli are not uniform. Also, the perception and interpretation of, and response to, the pain experience may be inordinately complex in terms of the patient's physical and mental history. One may expect that patients' cooperation and integrity may range between wide limits, and that their interpretation of pain may be influenced more by fear and desire for analgesia than in the use of experimental subjects. Clinical algesimetry also

cannot be expected to differentiate between the following mechanisms in the relief of pain: (1) acceleration of healing, (2) alteration of pathology as an antiphlogistic effect, (3) reduction of cause (as with atropine in ulcers), (4) sedation or hypnosis modifying interpretation, (5) improvement of attitude about pain (as with euphorigenic or tranquilizing drugs), (6) elevation of the pain threshold, and (7) interruption of the afferent sensory pathway without a cortical component.

Development of this comparison of the problems of algesimetry, derived from reports and implications of many students of algesimetry and from personal experience, clearly demonstrates (to me, at least) that there is no single, completely adequate method for evaluating analgesics. It is evident also that utilization of all three methods cannot predict completely the efficacy of a new compound in all clinical situations.

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If agreement could be reached on the definition of what constitutes analgesia, better rapport could be achieved among algesimetricists, and between them and clinicians. If more attention could be paid to the mechanisms of pain and analgesia, and perhaps less to screening compounds, algesimetry might evolve into a far more precise science.

Care in assessing the reliability and validity of specific methods should be emphasized. Some methods in daily use have not as yet been carefully studied. Reliability is the ability to obtain similar results on more than one occasion, and validity is to confirm clinically what has been observed experimentally.

The enormous influence of suggestibility in the pain problem is perhaps the greatest obstacle to more similar reports from different laboratories working on similar compounds. It is also a great challenge to the investigator who attempts to control this factor.

Elsewhere in this symposium are expositions of radiant energy and clinical algesimetry by prominent authorities in those fields. It was my assignment to include some remarks on tooth-pulp algesimetry. What has been written above has come to serve as background material for the design and conduct of algesimetric experiments in my laboratory. Every effort has been made to conduct algesimetry as precisely as possible with maximal reliability and validity.

The tooth pulp is preferred as a stimulus site because it is known that pain is the only sensation perceptible from an adequately stimulated pulp. Additional advantage resides in the fact that the site is enclosed in an enamel vault which protects it from changes in external temperature, humidity, pressure, and chemical factors. Teeth stimulated experimentally contain metallic fillings which serve as permanently placed electrodes. This affords the advantage of a fixed electrophysical relationship between the electrode and the pulp, for all practical purposes. When changes occur, they are so slow that they do not influence observations taken within a few weeks' time. Bjorn has shown the importance of using fillings insulated from the gums by enamel in all directions and of having the enamel surfaces dry during stimulation. If these cautions are not observed, unpredictable portions of the applied current will short-circuit away from the pulp.

Electricity is the preferred stimulus because, in addition to the precision of control, measurement, and application, it appears more nearly to resemble physiologic circumstances than other stimuli. Unless stimulation is quite ex-

cessive, there appear to be no local reactions which might alter the response to subsequent stimuli.

Experience has shown that the stability of the threshold of an individual given no medication (or placebo) is constant and reliable for at least three hours.

We have also found that the reliability coefficient of data taken coincidently on two teeth of each subject is statistically significant, although the significance diminishes as the analgesic potency of the medication diminishes. In an effort to evaluate reliability, two experiments have been performed. In the first, Harris and Brandel[16] determined the effects upon tooth pulp threshold of oral medication with 64 mg. codeine phosphate, 0.6 Gm. acetylsalicylic acid plus 0.6 Gm. phenacetin, a calcium lactate placebo, and a "dry run." Thresholds were obtained on each of two teeth in each of 14 subjects 4 times at five-minute intervals before, and 7 times at fifteen-minute intervals after medication.

The increments from the average premedication threshold of each tooth were determined, in voltage, and coefficients of reliability calculated on the pairs of increments for each subject. After codeine, the coefficient was found to be 0.70; after placebo, 0.60; after the antipyretic, 0.45, and during the dry run, 0.39. There were 90 pairs of increments available for each of the above correlations.

The second reliability test was to compare the effect of 64 mg. oral codeine, given to the same 7 subjects during two different, double-blind studies. The coefficient of correlation of responses was 0.52, which affords a probability value of about 0.05.

Uniformity of performance has improved in our experiments as we have reduced the significance of the electrical impedance in the circuit through the subject. This has been accomplished by increasing the power of the generator and interposing larger and larger impedance (several megohms) between generator and subject. Maximal uniformity to date has been achieved with a square wave of 1 msec. duration at a frequency of 1 per second.

In animal and human experiments, the "double-blind" discipline is enforced so that neither operator nor subjects know the identity of the medication. Care is taken so that no visible, audible, or temporal cue to stimulation is given. Latin square design is employed in planning experiments so that if training is a factor, all compounds will appear equally often as first, second, third, etc., medicants.

There are several difficulties still to be overcome or endured in this methodology. One that may be overcome is whether increments in current necessary to elicit pain are properly expressed as absolute increments, or as proportions of the premedication threshold. Experiments to answer this question have begun. Perhaps this same question is in order in radiant-energy algesimetry.

Another question to be answered is: Should the increments of stimulus be on a logarithmic or linear scale? The "Weber-Fechner law" suggests that they should be logarithmic, but the radiant-energy experience indicates to the contrary.[10]

Though every effort is made to evaluate the responsiveness of subjects to placebos, it has been found by us and others[9] that the reaction of humans to placebos is not necessarily consistent. This problem will probably persist in all types of algesimetry.

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Attempts to validate tooth-pulp algesimetry have been difficult and, at best, are circumstantial. Early failure to detect a threshold elevation after 10 gr. of acetylsalicylic acid was discouraging, but this has been confirmed by others,[5,11-14] using the same or radiant energy techniques. Some confirmation (validation) of these findings is found in another explanation of the clinical success and algesimetric failure of salicylates.[15] It was postulated that aspirin relieved pain, in usual clinical dosage, by reducing inflammatory edema. Testing of this hypothesis progresses, with the bulk of evidence thus far confirming the idea.

Our findings that codeine orally did not elevate the threshold, but given parenterally did, also left validation in question.[16] Recent confirmation of this observation in clinical algesimetric studies lessens the doubt.[17]

Finding a new, clinically untried analgesic to be potent algesimetrically with subsequent confirmation in clinical use would seem to be the strongest validation yet available.

Operating on this premise, experience with Daprisal* appears further to validate tooth pulp algesimetry. This preparation was tested on humans by tooth pulp algesimetry before any clinical evidence was available. In one study[18] on 16 subjects, the threshold to experimentally induced pain was statistically more elevated than after a placebo, 324 mg. aspirin and acetopheneditin, and a dry run. In a second study,[19] on 15 different subjects, Daprisal orally was followed by an elevation of the threshold, which was statistically greater than the effect of 32 mg. codeine, or 32 mg. codeine + 32 mg. caffeine + 227 mg. acetysalicylic acid + 162 mg. acetopheneditin.

Noteworthy also, was the similarity of the average postmedication threshold increments after Daprisal, obtained in the two studies. Clinically, Daprisal has been found to be an analgesic.

It seems then, at this writing, that tooth pulp algesimetry affords reliability and reasonably good validity. If a compound relieves clinically occurring pain, it need not necessarily elevate the pain threshold, but if a compound elevates the pain threshold, it should relieve clinically occurring pain. Experience with aspirin exemplifies the former statement, Daprisal the latter.

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*Smith, Kline & French Laboratories. Each tablet contains dextro-amphetamine, 5 mg.; amobarbital, 32 mg.; acetylsalicylic acid, 0.16 Gm.; and phenacetin, 0.16 Gm.

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THE SEARCH FOR NEW ANALGESICS

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IT IS one hundred and fifty years since the first isolation of morphine from opium[1,2] and almost as long since the recognition of codeine as another of the natural opium alkaloids.[3] Codeine was tried in clinical medicine almost immediately[4] but was little used for about fifty years. Physicians, too, generally preferred opium to morphine until the means for parenteral administration were discovered and put into use.[5] There were indeed many assertions during this period of the superiority of opium over morphine and the inability of the latter to accomplish fully the medicinal benefits of opium.[6] Even to-day Pantopon retains a certain popularity, though there is no unequivocal evidence of a more than additive effect of the minor alkaloids.

The first artificially produced derivative of morphine appears to have been apomorphine[7]; chlorocodide was reported to be a product in the same reaction. A little later Pierce[8] described the effects of some acetylated derivatives of morphine and codeine. From the degree of activity shown it is unlikely that any one of these was diacetylmorphine (heroin) though two compounds were called α- and β-diacetylmorphine. The next step was the production of ethylmorphine (dionin) known at that time as codethyline.[9]

Early papers of note, which compared some fourteen derivatives with morphine, particularly with respect to narcotic, convulsant, and toxic properties, were those of Dott and Stockman.[10,11] They made no reference to analgesic action but the report was interesting because they compared compounds in which different groups (methyl, ethyl, amyl, benzoyl) had been substituted for H of the phenolic hydroxyl, because they compared mono- and diacetylmorphine, as well as quaternary salts, and because of their general conclusions. The authors said, "It seems certain that so long as the chemical changes are restricted to what may be called the outlying groups of the (morphine) molecule, very little alteration takes place in the physiological action. The change which does take place does not depend so much on the substituting body as on what part of the molecule is substituted. When a change is made in the kernel or groundwork of the molecule, then the action is much more profoundly altered."

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Attention began to be focused on improvement in therapeutic effectiveness when diacetylmorphine (heroin) was introduced into clinical medicine.[12-14] The claims for it, increased effectiveness plus decreased respiratory depression and decreased addiction liability, were in the latter respects erroneous[15]; but it gained rapidly in popularity, became eventually the drug of choice in the illicit drug traffic, and is still considered in some quarters indispensable. The next thirty years saw much work on elucidation of the morphine structure, intensive investigation of the pharmacologic action of morphine itself, but the introduction of comparatively few new morphine derivatives. Worth mentioning, however, are dihydrocodeine,[16] dihydromorphine,[17] dihydrocodeinone,[18] dihydromorphinone,[19] and dihydrohydroxycodeinone,[20] all of which were tried clinically in Germany during this period.

Thus we come to the inauguration in 1929 of the comprehensive program of chemical, pharmacologic, and clinical investigations in this field by the Drug Addiction Committee of the National Research Council, a program actively pursued to June 30, 1941. The work of the several laboratories cooperating resulted in many publications eventually gathered into a single volume,[21] and has been reviewed on a number of occasions,[22-24] most recently in a report for the United Nations.[25] Nearly 150 morphine derivatives were prepared and examined and twice that number of compounds were synthesized starting from simpler nuclei. The final report of the Drug Addiction Committee said, "The systematic scientific program has resulted in the accumulation of much affirmative data on two major problems: First, the quantitative dissociation of components of the complex morphine effect on the living organism by chemical modification of the morphine molecule; and, second, the development of compounds with definite analgesic action by suitable additions to simple nuclei. With respect to the first problem these examples will illustrate the results obtained. In amyldihydromorphinone, toxic, narcotic and respiratory effects were greatly increased, analgesic and emetic effects were decreased. In dihydrodesoxymorphine-D (desomorphine), without important change in toxicity, narcotic effect was increased five times, analgesic effect three times, euphoric and respiratory effects ten times, while emetic action was suppressed and addiction liability was decreased only slightly. In methyldihydromorphinone (metopon) analgesic action was increased more than narcotic and euphoric effects, emetic action was suppressed and there was a significant decrease in addiction liability and in the rate of development of tolerance. The last example is especially noteworthy because it represents an entirely new type of chemical modification of the morphine molecule."

In the latest review of this work[25] which covered the effect on analgesic action of all important modifications of the morphine molecule, these changes were categorized and a number of generalizations outlined, as follows:

1. Either the phenolic hydroxyl at position 3 of the morphine molecule (Fig. 1) or the alcoholic hydroxyl at position 6 is converted readily to an ether or ester. Also, the alcoholic hydroxyl has been substituted by chlorine, oxidized to a ketone or replaced by hydrogen. A free phenolic hydroxyl enhances, a free alcoholic hydroxyl interferes with, analgesic activity.

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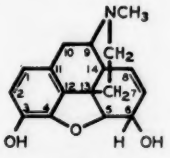
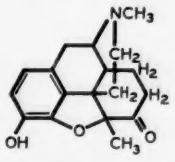
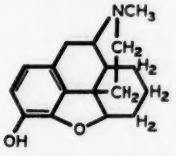
2. Removal by hydrogenation of the 7-8 double bond in the alicyclic ring has a variable effect on analgesic action; usually there is an increase, but it depends in some manner on the rest of the molecule.



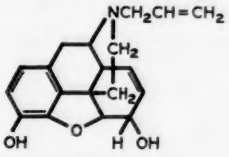
MORPHINE



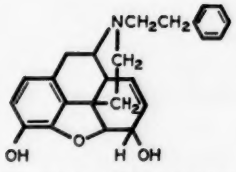
METHYLDIHYDROMORPHINONE
(METOPON)



DIHYDRODESOXYMORPHINE-D
(DESOMORPHINE)



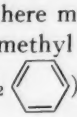
N-ALLYLNORMORPHINE
(NALORPHINE)



N-PHENETHYLNORMORPHINE

Fig. 1.

3. Morphine has a tertiary nitrogen carrying a methyl group in a piperidino-like ring structure. The tertiary character of the nitrogen, the methyl substituent and the ring structure are all intimately associated with analgesic action, because disruption of any one of these characteristics markedly reduces, in many instances practically abolishes, analgesic action. If the N-alkyl substituent consists of a 3-carbon chain, as in N-allylnormorphine (nalorphine), for example, with or without an additional methyl group in branched form, not only is the analgesic action virtually lost but the compound antagonizes or is able to suppress the analgesic action of morphine or of other morphine-like analgesics.[26-28] In man nalorphine may have some analgesic effect; at least it could be given with morphine without loss of the analgesic power of the latter.[29] It was dysphoric rather than euphoric in post-addicts and interfered with the euphoric effect of morphine.[30] Repeated administration of morphine-nalorphine mixtures may diminish to some extent the development of physical dependence.[31]

Recent unpublished work indicates that there may be an exception to the disadvantageous effect of substituting the N-methyl group of morphine, since if it is substituted by phenylethyl ($-CH_2CH_2$ ), analgesic effect is not decreased but is considerably enhanced.[32]

4. The addition of new substituents to the aromatic or alicyclic portions of the morphine molecule generally results in a decrease in analgesic effectiveness, but there are some notable exceptions. Methyl added to dihydromorphinone, for example at position 5 (or 7), producing metopon, or the addition of an hydroxyl at carbon 14, producing dihydrohydroxycodeinone or dihydrohydroxymorphinone, increases activity significantly. The last-named compound is one of the newest additions to the morphine family and is noteworthy because its duration of action seems to be the same as that of morphine and it is more rapid in its onset of effect. In nearly all other instances of increased analgesic activity in a morphine derivative duration of action is decreased considerably. Desomorphine has a potency approximately the same as that of dihydrohydroxymorphinone but its duration of action is not more than half as long.

5. Opening the oxygen bridge of the morphine molecule appears to decrease analgesic activity, but a decrease in effectiveness when the oxygen bridge is absent is more clearly seen in the morphinan series (see below).

A practical result of the years of cooperative effort under the Drug Addiction Committee, in addition to the accumulation of data on structure-action relationships, was the production of metopon, which was shown to be as effective orally as subcutaneously.[33] In spite of difficulties in preparation the morphine-producing firms of this country at the suggestion of the Committee undertook the manufacture of metopon and it became available commercially in the spring of 1947. The Committee supervised its distribution for a year limiting its use to the relief of pain of malignant disease. Reports on its use in more than 4,000 cases were received from which it was concluded that, "Metopon hydrochloride is an effective oral analgesic for chronic pain, the use of which is accompanied by a high incidence of mental clarity and a low incidence of side-reactions. Tolerance to metopon develops more slowly than tolerance to morphine."[34] Metopon after the first year became available as any other narcotic but continued to be marketed in a form for oral administration only.

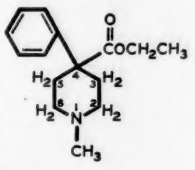
In the late 1930's, German chemists were looking for a synthetic spasmolytic agent as a substitute for atropine. One product of this research was shown incidentally to have significant analgesic effect[35] and, subsequently, other morphinelike properties.[36-38] This was 1-methyl-4-phenyl-4-carbethoxypiperidine (Dolantin, Demerol, meperidine, pethidine, etc.). Thus a by-product of one investigation became the first wholly synthetic analgesic compound with an activity at all comparable to that of morphine. After the fact, i.e., after the demonstration of the analgesic action of meperidine, Schaumann[38] related its structure to that of morphine by pointing out the presence in the latter of an N-methylphenylpiperidine moiety.

Schaumann[38] reported upon 41 compounds related to meperidine, and others[39-42] have described many other compounds in this series. Again certain generalizations are possible[25] (see Fig. 2 for meperidine structure):

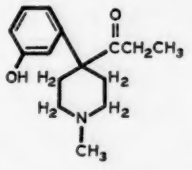
1. A phenyl group attached to the quaternary carbon (carbon 4) was optimal if not the essential formulation, since shift in position, substitution or removal of the phenyl group reduced activity.

2. A substituent, perferably OH, on the phenyl group *meta* to the piperidine ring linkage, a relation which corresponds to the position of the phenolic hydroxyl group at position 3 in morphine, increased analgesic action.

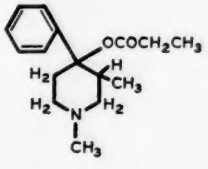
3. Removal of the methyl group or its replacement by larger alkyl groups reduced analgesic effectiveness; nor could the nitrogen be changed from tertiary to quaternary without loss of analgesic action. Very recently the surprising discovery has been made that, if the substituent on nitrogen was a ring structure, phenyl or morpholinyl, separated from the nitrogen by CH_2CH_2, analgesic activity was increased several fold.[43]



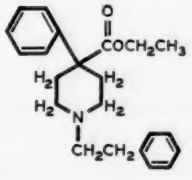
1-METHYL-4-PHENYL-4-CARBETHOXYPIPERIDINE (PETHIDINE, MEPERIDINE)



1-METHYL-4-(*m*-HYDROXYPHENYL)-PIPERIDINE ETHYL KETONE (KETOBEMIDONE)



α-1,3-DIMETHYL-4-PHENYL-4-PROPIONOXYPIPERIDINE (ALPHAPRODINE)



1-(2-PHENYLETHYL)-4-PHENYL-4-CARBETHOXYPIPERIDINE

Fig. 2.

4. With respect to the addition of a substituent to the piperidine ring only a methyl group at position 3 increased analgesic activity significantly.

5. Increasing or decreasing the size of the heterocyclic ring or opening the ring decreased analgesic effectiveness.

6. The effects of changing the carboxylate portion of the molecule were variable but mostly in the direction of decreased action. The change of the ethyl carboxylate to an ethyl ketone, when there was also an hydroxyl in *meta* position on the phenyl group (ketobemidone), or to propionoxy, when there was a methyl group at position 3 of the piperidine ring (alphaprodine) increased analgesic effect markedly. In ketobemidone, addiction liability was increased even more than analgesic action[44,45]; it produced intense physical dependence very rapidly. With alphaprodine the greater analgesic effectiveness was of significantly shorter duration.[46]

The study of analgesic activity and particularly investigation of the relation of effectiveness to chemical modification in new agents has been greatly facilitated by improvements in methodology. We have reviewed the older methods previously.[47] For the most part they were able to distinguish only the presence or complete absence of sensation. Almost thirty years ago we made an attempt

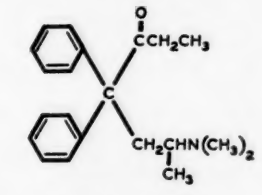
to devise a method by which one could determine degrees of decreased sensitivity as well as complete analgesia.[48] This method employed calibrated pressure applied to the tip of the cat's tail. Others adapted the principle to the mouse[49] and to the rat.[50] A distinct advance was achieved by Hardy, Wolff, and Goodell[51] when they described the measurement in man of the pain threshold to thermal radiation. Most subsequent investigators who have tried their method in man have abandoned it as unsatisfactory probably because of the impossibility of controlling disturbing factors except in highly trained subjects. Nevertheless the method has been adapted to animal experimentation and the principle is in regular use in some form in many laboratories. Radiant heat focused on the blackened skin surface causes a characteristic tail-flick in the rat[52-54] or a skin-twitch in the guinea pig[55] and the dog,[56] and an increase in reaction time of the response seems in each species to parallel analgesic activity. Perhaps the most satisfactory adaptation is that of Winter and Flataker[54] since it measures "total analgesic effect," taking into account the degree of deviation in reaction time and the duration of such deviation after drug administration. Each of the animal radiant heat methods, however, measures a spinal reflex, and similar responses are obtained before or after drugging in intact and spinal animals.[57]

Woolfe and Macdonald[58] in 1944 described a simple method for evaluation of analgesic action in mice in which the animal was dropped onto a hot plate and its reaction to the heat stimulus was measured. The behavior of the animal on the hot plate suggested that its reaction was a whole animal response rather than a spinal reflex. Besides Herr and his associates[59] have shown that the hot plate response, unlike the tail-flick, was not obtainable in a spinal animal. We have elaborated the hot plate method,[60] patterning the procedure on bioassay methods, employing both the degree of deviation in post-drug reaction time and the duration of such deviation for determination of analgesic effect and using the per cent of animals affected at graded doses to calculate an ED_{50}. The ED_{50}, dose significantly affecting 50 per cent of the animals, plus a figure for duration of effect, seems to us to give the best over-all picture of analgesic action for comparison of one agent with another.

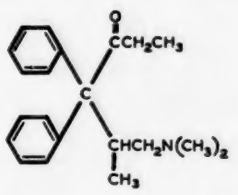
The survey of German chemical industries in 1945[39] revealed that German chemists had again made a most important advance in the development of a synthetic analgesic. The product discovered was methadone, 6-dimethylamino-4,4-diphenyl-3-heptanone. It apparently differed very significantly from morphine or meperidine in structure, but was shown by many investigators to be capable of producing in man and animals practically all of the characteristics of morphine action, including, unfortunately, tolerance and addiction properties; and to be equivalent to morphine, milligram for milligram, in analgesic potency.[61-63] The German chemists made many methadone derivatives.[39] We have reported the examination of many of them for analgesic effectiveness,[64] including all of the alcohols and acetates which could be derived from methadone, isomethadone, and their isomers.[65] The report to the United Nations,[25] already referred to, tabulated more than 200 methadone derivatives.

According to the method of synthesis, methadone or isomethadone may be the predominant or sole final product. These two compounds differ only with

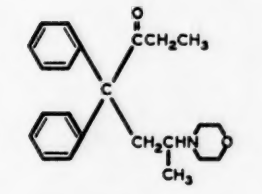
respect to the position of one methyl group (Fig. 3). Methadone is the stronger analgesic. Both compounds are synthesized as racemates, both have been resolved to their optical components, and in both cases analgesic activity is exhibited almost entirely by the levo-isomers. The relatively nonanalgesic dextro-isomers have little or no addiction liability. The levo-isomer of isomethadone is, milligram for milligram, equivalent to methadone or to morphine as an analgesic and produces the fewest undesirable side effects in man.[66,67]



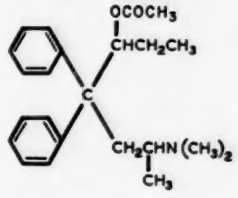
6-DIMETHYLAMINO-4,
4-DIPHENYL-3-HEPTANONE
(METHADONE)



6-DIMETHYLAMINO-4,
4-DIPHENYL-5-METHYL-3-
HEXANONE (ISOMETHADONE)



6-MORPHOLINO-4,
4-DIPHENYL-3-HEPTANONE
(HEPTAZONE)



∝-*l*-6-DIMETHYLAMINO-4,
4-DIPHENYL-3-ACETOXYHEPTANE
(∝-*l*-ACETYLMETHADOL)

Fig. 3.

Practically all changes in the amine of methadone or isomethadone, except substitution of $N(CH_3)_2$ by morpholine in the compound heptazone,[54] decreased analgesic activity; increasing or decreasing the number of carbons between the phenyl groups and the amine decreased activity; and addition of a substituent to, substitution, removal or shift in position of a phenyl group decreased activity. If the ketone was changed to an alcohol in all but one instance, decreased analgesic effect resulted but subsequent acylation of the alcohol restored activity, equal to or greater than that of the ketone, whether the changes were effected in the methadone or isomethadone racemates or in their optical isomers. In some instances, particularly *α-l*-acetylmethadol derived from *d*-methadone, the new acylated derivative had a very prolonged action and was more effective when given orally than subcutaneously.[65]

With the development of the methadone series of compounds it again became apparent, as in meperidine and, reasoning backwards, also in morphine derivatives, that a phenyl group, a quaternary carbon, and a tertiary amine at a suitable distance are optimal if not essential characteristics for analgesic action.

For many years many chemists sought to prove by synthesis the constitution of morphine, and ultimate success was attained only quite recently by Gates and his associates.[68] This was an outstanding scientific achievement, but for the greatest analgesic effectiveness complete synthesis was not necessary. Grewe[69] had previously reported the synthesis of N-methyl-morphinan (Fig. 4) (the basic

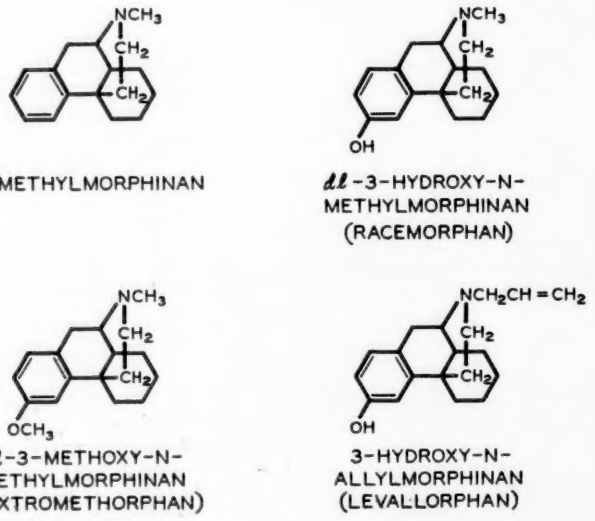
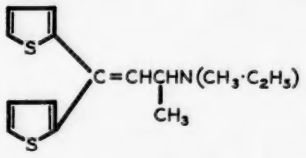


Fig. 4.

ring structure of morphine minus the oxygen bridge) and that it had some analgesic effect. Schnider and Grüssner[70] in 1949, and Grewe[71] very shortly thereafter, reported the synthesis of 3-hydroxy-N-methylmorphinan (racemorphan), a step nearer the structure of morphine, which had greater analgesic action than the natural alkaloid. Resolution of racemorphan again placed the analgesic effectiveness with the levo-isomer. The dextro-isomer had no analgesic effect and no addiction liability.[72] The methyl ether, 3-methoxy-N-methylmorphinan (racemethorphan) was a more effective analgesic than codeine. Its levo-isomer was again the active component; the dextro-isomer had no analgesic action or addiction liability[71] but was shown recently to be effective as an antitussive.[73,74] The N-allyl analog of racemorphan (levallorphan) was an antagonist to morphine and related substances[28] and the N-phenethyl derivative (*l*-3-hydroxy-N-phenethylmorphinan) was several times more potent as an analgesic than levorphan.[32]

It will be noted that 3-hydroxy-N-methylmorphinan is most closely related to desomorphine (Figs. 1 and 4) differing from the latter only in the absence of the oxygen bridge. The former, however, was less effective as an analgesic in man and animals but the duration of its action was at least that of morphine, whereas the duration of action of desomorphine was much shorter.

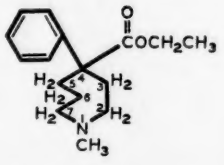
A very interesting development in synthetic analgesics is the demonstration of morphine-like activity in a group of dithienylbutenyl derivatives.[60,75,76,77] These compounds do not contain a phenyl group, but rather, isosteric thienyl groups (Fig. 5), and there is no true quaternary carbon. The thienyls are connected with a central carbon, which might be called quasi-quaternary since none of its valences are connected with hydrogen, and are separated from a tertiary amine by two carbon atoms. The most active member of this group was one in which the amine was methyl-ethyl, namely, 3-methyl-ethylamino-1, 1-di-(2′-thienyl)-but-1-ene. It was at least as active as morphine in laboratory animals, but less effective in man.[78] It produced, nevertheless, morphine-like subjective reactions in man and has addiction liability.



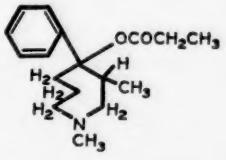
3-METHYLETHYLAMINO-1,1-DI-(2′-THIENYL)-BUT-1-ENE

Fig. 5.

Still another recent development in this field was the production of a group of compounds differing from meperidine and its derivatives only in having a seven-membered heterocyclic ring in place of the six-membered piperidine. These were the hexamethyleneimines (formerly described as azacycloheptanes). The first of the series was the meperidine analog, 1-methyl-4-phenyl-4-carbethoxy-hexamethyleneimine (Fig. 6).[79,80] This was a poorer analgesic than meperidine



1-METHYL-4-PHENYL-4-CARBETHOXY-HEXAMETHYLENEIMINE

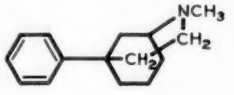


1,3-DIMETHYL-4-PHENYL-4 PROPIONOXYHEXAMETHYLENEIMINE

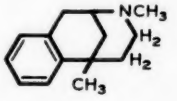
Fig. 6.

in animals and man. Other hexamethyleneimines seemed to bear a similar relationship to the comparable members of the meperidine series. The most recently made derivative, however, 1,3-dimethyl-4-phenyl-4-propionoxyhexa-methyleneimine, the analog of alphaprodine (Nisentil) is at least as active as the latter in animals.[32] It is now being tested for addiction liability.

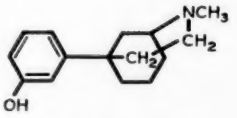
Our chemists have been synthesizing a series of phenylmorphan and benzmorphan derivatives (Fig. 7),[81-83] with very promising results. The two comparable compounds, Nos. 5754 and 6048, had identical analgesic effectiveness, about half that of meperidine. Introducing an hydroxyl in position 3 of phenylmorphan (No. 7215) increased activity almost to that of morphine. The corresponding hydroxy derivative of benzmorphan is now being synthesized.



5754. 2-METHYL-5-PHENYLMORPHAN



6048. 2,5-DIMETHYL-6,7-BENZMORPHAN



7215. 2-METHYL-5-(*m*-HYDROXYPHENYL)-MORPHAN

Fig. 7.

Finally the present situation with respect to synthetic analgesics can probably be summed up best by two quotations. The first of these represents the conclusions of Braenden, Eddy, and Halbach[25] from their analysis of the relation of chemical structure to analgesic action. "The following features seem to stand out for known compounds posessing morphine-like analgesic activity: (a) A tertiary nitrogen, the group on the nitrogen being relatively small. (b) A central carbon atom none of whose valences are connected with hydrogen. (c) A phenyl group or a group isosteric with phenyl, which is connected with the central carbon atom. (d) Maximum activity is obtained when the central carbon atom is connected with the nitrogen by a two carbon chain. . . . the presence of these conditions cannot be made a basis for prediction of analgesic action. However, all substances which have justified the characterization of morphine-like analgesics conform to the above features." The second quotation is an opinion of the Committee on Drug Addiction and Narcotics of the National Research Council, expressed at its tenth meeting; namely, "all needs for morphine and related substances for symptomatic relief can be met by synthetics now known."[84] This does not say that synthetics are superior to the natural alkaloids, though some of them may be. The potent agents still produce the same sort of side effects as morphine and are addiction producing. Separation of analgesic action and addiction liability in substances having the same or greater potency than morphine has not been attained.

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POSTOPERATIVE PAIN: RESEARCH AND TREATMENT

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THE pathetically grim and perspiring patient, fearful of moving or breathing, has become a constant fixture in postsurgical wards. His suffering was anticipated by his physicians and is accepted in the knowledge that it will disappear in time. This is the expected, the usual, and the inevitable postoperative pain—the most frequent and most neglected painful state in the hospital situation.[1] A recent survey of narcotic practices in a large general hospital disclosed that two-thirds (65.9 per cent) of all doses of narcotics dispensed for inpatients were used on the surgical services and, of these, three-quarters were used in the treatment of postoperative pain.[2]

In the course of studies designed to determine the potency of newer analgesic drugs, we and others (vide infra) have had the opportunity to follow closely several thousand postoperative patients from the time of operation until at least the second postoperative day. The complaints of these patients and their modification by drugs were recorded by technicians who observed these patients both day and night. Much of the data presented here were collected in this manner. They will be used to: (1) describe some of the characteristics of postoperative pain; (2) indicate how, by appropriate experimental design, this ready source of clinical pain can be used for research, with the results of such investigations, and (3) apply these observations to the rational treatment of postoperative pain.

SOME CHARACTERISTICS OF POSTOPERATIVE PAIN

There are many misconceptions among physicians as to the severity of pain which follows certain surgical procedures, and more especially to the relative efficacy of various drugs in its treatment. These "clinical impressions" are prevalent because nurses, not physicians, treat postoperative pain. Observations made by nurses are often based on criteria which do not necessarily coincide with good medical practice. Much of what is believed to be known about postoperative pain is the result of such observations as recorded in nursing notes.

Incidence.—Periodically, investigators who use postoperative patients for their studies rediscover that many patients do not have pain following surgery. Papper, Brodie, and Rovenstine[3] found that 44 per cent of their 237 postoperative

patients failed to complain of pain. Included in this group were 108 patients who had had intra-abdominal or intrathoracic procedures, and, of these, 27 per cent did not complain of pain. Jaggard, Zager, and Wilkins[4] found that 36 per cent of 1,005 patients received no narcotics during the entire postoperative period. Our experience has been similar. For example, 21 per cent of 104 patients who had undergone either a gastrectomy or colectomy received one or no dose of narcotic during the entire postoperative period. A more general appreciation that pain does not invariably follow surgery would prevent statements as to the therapeutic efficacy of certain drugs or anesthetic techniques based on uncontrolled observations of the infrequency of postoperative pain. An example of this was the unfounded popularity enjoyed by intravenous procaine.[5]

Occurrence.—The number of doses of narcotic required by a group of postoperative patients is a useful index of the severity of pain experienced. In the course of our studies it was observed that certain operative procedures were followed by little or no demand for analgesics, in contrast to intra-abdominal or intrathoracic procedures. A partial list of such operative procedures is given in Table I, representing our general experience but acknowledging occasional individual patient exceptions. The paucity of pain following these procedures has been confirmed in the data of others.[4,6] Papper, Brodie, and Rovenstine[3] found that 58 per cent of patients having surgery of the superficial parts of the body did not complain of pain after operation, in contrast to only 27 per cent for those having abdominal or thoracic surgery.

TABLE I. SURGICAL PROCEDURES FOLLOWED BY MINIMAL POSTOPERATIVE PAIN

Surgery of head and neck, including thyroid
Surgery of hand and wrist
Surgery of vagina
Surgery of penis and scrotum
Amputation
Skin graft
Mastectomy
Incision and drainage of abscess
Vein stripping or ligation
Closed reduction of fracture
Hip nailing
Burn dressing
Transurethral resection

Symptoms.—Pain is but one of the symptoms of the postoperative patient. The complaints recorded before 117 successive administrations of morphine are listed in Table II. In all these instances pain was the chief complaint. However, these patients may complain bitterly and primarily of symptoms such as sleeplessness, discomfort from gastric tube or oxygen catheter, sore throat, headache, backache, uncomfortable position in bed, bladder discomfort from indwelling catheters, or tightness and weightiness of casts. These symptoms as primary complaints are responsible for 10 to 15 per cent of all requests for medication. Obviously, many can be treated without morphine.

TABLE II. POSTOPERATIVE SYMPTOMS PRIOR TO 117 ADMINISTRATIONS OF MORPHINE IN 43 PATIENTS

SYMPTOM	FREQUENCY (PER CENT)
Steady wound pain	91
Increased pain on motion	99
Nausea or vomiting	47
Headache	19
Crampy gas pains	3
Restlessness or anxiety	91

Pain on motion, breathing, or coughing is common (Table II) and is difficult to relieve. When it is the primary symptom, the administration of morphine (10 mg. per 70 Kg. of body weight) will result in relief in only 47 per cent of the instances (based on 55 doses). In contrast, this dose of morphine will relieve steady-wound pain in 74 per cent of the instances (based on 166 doses). When both occur together, as is usual, relief of the steady-wound pain is accompanied by comfort or satisfaction of the patient.

Duration.—Pain of severity sufficient to require narcotics usually disappears within forty-eight hours following surgery. The usual time course of such pain is indicated in Table III, where the frequency of narcotic administration by time postoperatively is used as the index. It is apparent that the first twenty-four hours following operation are the most difficult. There is little need for narcotics after forty-eight hours. Exceptions to this usual time course are present in patients who develop certain surgical complications, e.g., infection, and in patients who develop psychic dependence on the drugs or the injection per se or the associated care. Such exceptions are rare. Pain of lesser magnitude may persist for variable periods following operation and is readily controlled by nonnarcotic analgesics.

TABLE III. FREQUENCY OF MORPHINE ADMINISTRATION DURING EIGHT-HOUR PERIODS FOLLOWING 60 MAJOR INTRA-ABDOMINAL SURGICAL PROCEDURES

NARCOTIC DOSES	HOURS POSTOPERATIVELY							
	0–8	8–16	16–24	24–32	32–40	40–48	48+	TOTALS
Number	57	58	39	41	18	18	34	265
Per cent	21.5	21.9	14.7	15.5	6.8	6.8	12.8	100.0

Relation to Patient Variables.—We have repeatedly attempted to correlate the severity of postoperative pain with certain characteristics of the patients themselves.[7] These efforts have been largely unsuccessful except for the lack of pain following certain surgical procedures listed above. No great differences exist between a variety of major surgical procedures in their ability to produce postoperative pain (Table IV). We have found no linear correlation with age

despite the common observation that the very young and very old seem to experience less pain following identical surgical procedures. In the young this may be the result of lesser degrees of association between pain stimuli and fearful consequences, whereas in the aged (over 70 years) it may be a consequence of the more debilitating effects of anesthesia and surgery on these patients. We have not been able to relate the degree of postoperative pain to sex, type of anesthetic, duration of anesthetic, previous medical history, previous surgical history, previous hospitalizations, obvious personality types, noticeable personality disorder, or presence of preoperative pain. Pain following surgery seems to be random with regard to obvious patient characteristics.

TABLE IV. RELATIONSHIP OF SURGICAL PROCEDURE TO NARCOTICS RECEIVED DURING FIRST 30 POSTOPERATIVE HOURS

OPERATION	NUMBER OF PATIENTS	MEAN DOSES OF NARCOTIC ± S.E.	RANGE
Colectomy	44	3.14 ± 0.29	0–7
Hysterectomy	57	3.67 ± 0.20	0–7
Gastrectomy	54	4.00 ± 0.43	0–9
Pyelolithotomy	47	3.23 ± 0.32	0–7
Pneumonectomy	25	3.68 ± 0.42	0–7
Cholecystectomy	57	3.29 ± 0.26	0–7
Surgery of foot	44	3.59 ± 0.34	0–12
Laminectomy	38	4.89 ± 0.44	0–12
Surgery of knee	17	3.82 ± 0.57	0–8

Beecher[8] has observed that only one-fourth of seriously wounded soldiers admitted to a Forward Hospital complained of pain. He has recently contrasted this to a series of similar civilian wounds (surgically produced) in which three-fourths of the patients complained of pain.[9] In an attempt to explain this difference, he found no correlation between the incidence of pain and the size of the wound, the age of the patient, the anesthetic used, or the history of chronic or acute disease. He postulated that this difference in incidence of pain may be accounted for by the anxiety-relieving nature of a war wound (the end of combat and return to the safety of a hospital) in contrast to the anxiety-producing nature of civilian wounds (the implications of serious disease). This implies that the anxiety associated with pain stimuli is a significant determinant of the degree of pain. In this regard, it is of interest that Hill, Belleville, and Wikler[10] have demonstrated that morphine is much more effective than pentobarbital in relieving the anxiety produced by anticipation of pain.

Response to Placebo and Suggestion.—A subcutaneous injection given by a nurse to a patient in pain suggests that the drug is for pain and that relief will follow. We have on occasion observed good pain relief to follow injections of such drugs as penicillin. In a recent series of 293 postoperative patients who were given alternate injections of normal saline and a narcotic in treatment of their pain, no less than 43.2 per cent of 493 doses of saline resulted in pain relief. All patients had had major surgery and all doses were given within thirty hours of operation. This frequency is in accord with the experience of others.[11,12] However, in the 69

patients studied by Lasagna and his associates, only 14 per cent obtained pain relief from every dose of placebo and 31 per cent consistently failed to get relief. The remainder responded inconsistently.

In the studies mentioned above, no positive suggestion as to pain relief accompanied the injection of placebo other than that implicit in giving an injection in the presence of pain. An attempt was made (in collaboration with Beecher at the Massachusetts General Hospital) to estimate the effect of explicit suggestion, both positive and negative, in a small number of patients. Twenty-seven patients experiencing steady wound pain were told they were to receive a wonderful new drug which would completely take away their pain. They were given saline intravenously and one-third reported pain relief. Twenty-one similar patients were told that they were to receive an injection of a new drug which was not very good. They were told that their pain would probably not be relieved, but after one hour they would be given an injection that would certainly take away all their pain. These patients were given morphine first, then saline. Four of these patients reported no improvement in their pain, or even an increase in pain, after 10 mg. of morphine intravenously, but were completely relieved by saline one hour later. It would seem that suggestion can operate in the relief of pain.

RESEARCH

At first glance, the unpredictability of postoperative pain and the multitude of patient variables which cannot be controlled would seem to preclude the use of postoperative pain for research. However, the recognition that many patients do not have pain, that much pain can be relieved by placebos, and the assumption of a random distribution in the severity of postoperative pain with regard to measurable patient characteristics enable study of this ready source of clinical pain by proper experimental design.

Experimental Design As Applied to the Study of Analgesic Drugs.—The problem of determining with precision the analgesic potency of drugs has long been a difficult one. It would seem that potency could readily be determined by any of numerous available methods which produce pain in animals or in man and measure its relief by drugs. However, these methods consistently fail to yield information of any greater accuracy (and often less) than that of the uncontrolled clinical trial. The uncontrolled clinical trial requires large numbers of patients, many observations, much time, and yields results that are not reproducible.

A technique[7] has been devised which circumvents most of these difficulties by controlling the recognizable patient variables and makes possible the use of clinical pain for experimental purposes. The chief innovations of this technique are:

1. Establishment of a reference standard for analgesic potency in man to which new drugs may be compared. We have used saline, morphine (10 mg./70 Kg.), or meperidine (50 mg./70 Kg.) as the standard.

2. Alternation of the new drug to be studied and the standard in individual patients, controlling patient variables. The first drug administered is similarly alternated, controlling time variables.

3. Elimination of bias by having both the subject and the observer ignorant of the drug administered.

The principles pertaining to measurements of subjective responses such as pain, which have been employed here, have been described in detail by Beecher.[13] In practice, trained technicians evaluate the effectiveness of each medication. Since the drug names are coded and the code is changed frequently, observer bias is minimal.

Several dose levels of the new drug are compared to the same standard, and the differences in incidence of pain relief between the drug studied and the standard are plotted as a dose-effect curve. The dose of new drug which will produce analgesia equivalent to that of the standard can then be readily estimated. Such a hypothetical dose-effect curve is shown (Fig. 1), in which the equivalent analgesic dose is calculated to be about 65 mg. Having established the equivalent analgesic dose, the drug is then given to normal subjects to determine the frequency and severity of side actions.

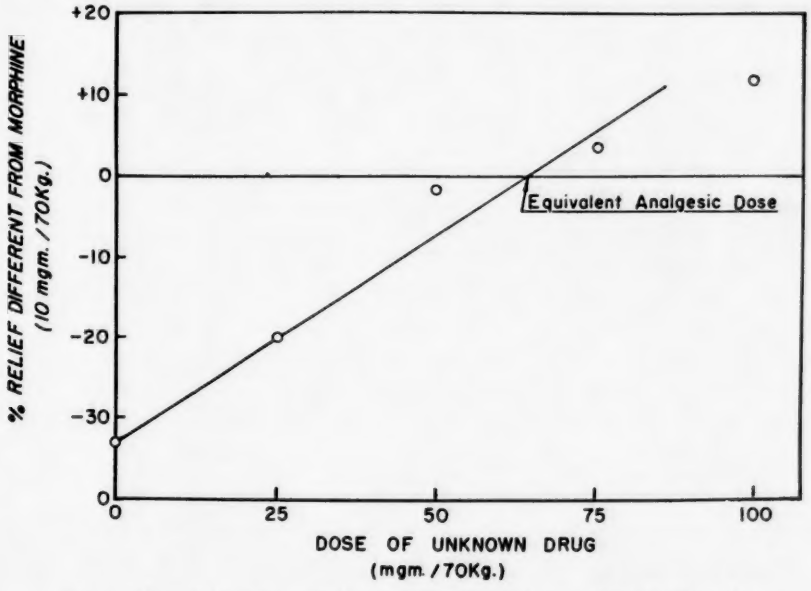

Fig. 1.—Hypothetical dose-effect curve indicating that approximately 65 mg. of unknown drug is the analgesic equivalent of 10 mg. of morphine.

By appropriate modification of this experimental design, postoperative pain can be used to study the analgesic properties of therapeutic procedures not involving drugs, or to study pain mechanisms themselves. The postoperative situation can be similarly used for investigation of other subjective phenomena such as nausea, sedation, and anxiety. Notable work has already been achieved in studies of the placebo response in postoperative patients.[11]

Results of Studies of Analgesic Drugs.—Many drugs have been evaluated in the manner described. They are listed in Table V with their equivalent analgesic doses as well as the approximate equivalent doses of some drugs studied by ex-

tensive clinical trial. Except for the last three, these drugs have been administered to normal subjects and their side-action liability studied. Unfortunately, the incidence of side actions from all the drugs was approximately the same as that of 10 mg. of morphine. When used in doses producing equal analgesia, they depress respiration to the same degree and produce nausea and vomiting with the same frequency as morphine (with the possible exception of levo-isomethadone, which may produce nausea and vomiting less often than morphine). The subjective side-action liability of meperidine has not been completely evaluated. However, in 75 to 100 mg. dosage, meperidine is equally as depressant to the respiration as 10 mg. of morphine. The analgesic potency of codeine does not equal that of morphine, even at 120 mg., and at this dose codeine is a potent respiratory depressant.[16]

TABLE V. EQUIVALENT ANALGESIC POTENCY OF DRUGS STUDIED IN POSTOPERATIVE PATIENTS

DRUG	DOSE MG. PER 70 KG. OF BODY WEIGHT SUBCUTANEOUSLY
By Technique Described	
Morphine	10
l-Methadone[14]	5
dl-methadone[14]	10
l-isomethadone[14]	10
dl-isomethadone[14]	25–30
Heptazone[15]	50–60
6-methyl-dihydromorphine[15]	30
Metopon[15]	3
Meperidine[16]	75–100
Codeine[16]	120+
Nalorphine[17]	10
By Extensive Clinical Trial	
Racemorphan[18]	5
Levorphan[19]	2.5
Alphaprodine[20]	40

Nalorphine has been found to be a potent analgesic when administered to patients who have received no prior narcotic. It is also a respiratory depressant and tends to produce bizarre dreams approaching visual hallucinations when given to normal subjects. Isbell[21] has administered 80 to 100 mg. of nalorphine per day to former addicts for one month without observing withdrawal symptoms on cessation. The addicts expressed no craving for the drug and disliked it. It is possible that nalorphine is a long-sought nonaddicting potent analgesic.[17]

It has long been taught that barbiturates in less than anesthetic dose have little or no analgesic power. A study of the ability of 60 mg. and 90 mg. of sodium pentobarbital, given intravenously, to relieve postoperative pain has shown that this barbiturate produces analgesia with significantly greater frequency than a placebo.[22] Pentobarbital is not a potent analgesic, however, and does not approach the efficacy of morphine.

Oral Analgesics.—The postoperative situation is not ideal for an evaluation of oral analgesics because disturbances of gastrointestinal function are so common following operation. These disturbances result in unpredictable drug absorption and often, by the time gastrointestinal function returns to normal, pain is minimal. Despite this, the technique has been successfully applied to study the effectiveness of several analgesics given by mouth.[23] It was found that when morphine (10 mg.), codeine (60 mg.), aspirin (0.3 Gm.), and aspirin (0.6 Gm.) were given orally, the only effective analgesic was 0.6 Gm. of aspirin. Neither morphine nor codeine could be distinguished from a placebo under these circumstances. The ineffectiveness of morphine by mouth has been noted by others,[24] but without general appreciation of it. Presumably, this is the result of poor absorption. Codeine has been shown to be well absorbed from the intestine,[25] and there is no explanation for its low oral potency, which has also been confirmed by others.[26] It has been demonstrated[25] that 10 per cent of administered codeine is converted in the body to morphine, and possibly many of the actions of codeine can be explained by variations in the per cent which is converted. Because of the laborious nature of such studies, there have been too few investigations of this important aspect of practical therapeutics. Such studies are much needed.

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The Placebo Reactor.—The high incidence of pain relief from a placebo which was mentioned above has stimulated interest in the placebo response—how and why it occurs. It is indeed surprising that patients who have so real a cause for severe pain would obtain pain relief from an injection of saline. It is more surprising when one notes that postoperative pain is an acute syndrome and does not involve the conditioning factors and behavior patterns which develop in patients suffering from chronic pain. Lasagna and co-workers[11] have carefully studied a group of patients who consistently obtained pain relief from placebos and have compared them with a group who consistently failed to obtain relief. They found significant differences in the attitudes, habits, educational backgrounds, and personality structure between these patients. Yet it is most significant that these differences could only be delineated by extensive and careful psychologic techniques. The placebo reactor could not be identified by the casual observer, nor could predictions be made.

Most postoperative patients are not consistent placebo reactors or nonreactors, at times obtaining relief from placebo and at other times not. This introduces a temporal characteristic, apart from basic personality characteristics, in determining placebo response. This temporal characteristic may be dependent on such things as day or night, visiting hours, time from operation, and the implications of the patient's disease. These investigations have stimulated further studies of the effect of personality characteristics on drug action.[27]

TREATMENT OF POSTOPERATIVE PAIN

Drugs Used.—Because most patients suffer some disturbance of gastrointestinal function following operation either from the anesthetic or the surgical procedure itself, it is usually necessary that parenteral drugs be used. As indicated above, no drug which has been adequately studied has been found to produce the analgesia of morphine with less side action than morphine. Based on current information, all drugs listed in Table V (with the exception of codeine) will produce adequate postoperative analgesia if given in equivalent dose, and at

this dose the same side actions might be expected as with morphine. Morphine remains the standby in the treatment of postoperative pain. It is also less expensive than proprietary preparations. There is evidence that alphaprodine is significantly shorter in action than morphine, but this offers no advantage in the treatment of postoperative pain.

The Dose.—The characteristic dose-response curve of drug action applies to the analgesic properties of narcotics. An optimal dose can be determined, exceeding which further increases will not result in proportional increases in analgesia. For morphine in postoperative pain, this dose is 10 mg. per 70 Kg. of body weight. Table VI demonstrates the small additional analgesia obtained from a 100 per cent increase in the dose of morphine (10 mg. to 20 mg.). These data were obtained from alternate doses of morphine and placebo in the same patients. Analgesia is represented by the difference in incidence of pain relief. Lasagna and Beecher[28] have pointed this out with similar data and showed the significant increase in side actions such as nausea, vomiting, and respiratory depression, which occurs at higher doses in return for small additional analgesia. This pertains as well to narcotics other than morphine. For the average 150 pound man, 10 mg. of morphine is an adequate dose for relief of postoperative pain. This estimate excludes patients with unusually severe pain and patients who have developed tolerance or cross-tolerance to narcotics.

TABLE VI. RELATIONSHIP BETWEEN DOSE OF MORPHINE AND INCIDENCE OF ANALGESIA GREATER THAN A PLACEBO

DOSE PER 70 KG. OF BODY WEIGHT	NUMBER OF PATIENTS	NUMBER OF DOSES	% ANALGESIC DOSES GREATER THAN PLACEBO
5	56	109	25.7
10	38	71	35.2
15	31	59	37.3
20	18	40	37.5

Pain occurring earlier in the postoperative period is more difficult to relieve than that occurring after twenty-four hours. This was implied earlier (Table IV) by the increased incidence of narcotic administration within the first tweny-four hours following major surgery. Further data to support this were obtained by comparing the incidence of pain relief according to the order of doses of morphine (Table VII). Pain occurring immediately after surgery was most difficult to relieve. It would seem wise to treat postoperative patients with a high initial dose, then lower succeeding doses.

TABLE VII. INCIDENCE OF PAIN RELIEF BY MORPHINE ACCORDING TO ORDER OF POSTOPERATIVE DOSES IN 198 PATIENTS

Dose number	1	2	3	4+
Number of administrations	198	119	55	37
% Analgesic doses	62.6	84.0	87.3	89.2

Symptoms Other Than Pain.—Many of the associated complaints of postoperative patients can be readily improved by good nursing care. A comfortable position in bed, with frequent turning and other simple measures, will greatly improve the mental state as well as the "pain" of these patients. A lubricant containing a topical anesthetic applied to the gastric tube before insertion will prevent much of the irritation and annoyance of a nasogastric tube. Frequent checks to see that the bladder catheter is draining will relieve much bladder discomfort from indwelling catheters. In addition, we have found that intramusclar sodium pentobarbital, 100 mg. per 70 Kg., is a very useful adjunct to a narcotic for routine postoperative use in the treatment of sleeplessness, restlessness, anxiety, and nausea. In the presence of mild pain, it can serve as a substitute for morphine. Even when given in the presence of severe pain, we have rarely seen the excitement so often warned against.

Nursing Practices.—Since nurses do, in fact, treat postoperative pain, we have found that nursing practices as learned in school or as acquired later have a profound effect on postoperative treatment. For example, some nurses have been taught that every postoperative patient must have two doses of narcotics during the first postoperative night. Patients are therefore awakened to be given morphine. Some nurses routinely give all postoperative patients a narcotic at 11:00 p. m. to guarantee a quiet night and time for their other duties. Patients were often categorized as having "real" or "not real" pain, and given medications accordingly, despite a complete lack of correlation with placebo response.

We (Beecher and I, at the Massachusetts General Hospital) attempted to estimate the magnitude of some of these abuses by comparing the amount of morphine a specific group of patients needs to the amount actually received. Thirty patients who had uncomplicated cholecystectomies by standard operative procedures under ether anesthesia were allowed to receive 10 mg. of morphine as often as every hour to control their pain. For other complaints and minor discomforts they received pentobarbital. They were kept comfortable at all times and given drugs for as long as necessary postoperatively. For comparison, the hospital records of identical groups of ward, semiprivate, and private patients were randomly collected and the amount of postoperative morphine they received was tabulated. Any errors in this comparison would be in a negative direction since nurses may forget to record administrated narcotics. The mean doses of morphine per patient (± standard error) following cholecystectomies in these four groups were as follows:

Ward group studied:	3.2 ± 0.4
Ward group (hospital records):	5.6 ± 0.4
Semiprivate group (hospital records):	9.8 ± 0.7
Private group (hospital records):	13.4 ± 1.2

The number of doses of barbiturate were approximately the same in all four groups (1 to 2 doses per patient). When these data were broken down into time intervals following operation, it was found that in the private group 40 per cent of the total narcotics were administered after forty-eight hours following surgery. Although there are undoubtedly many psychosocial implications in these data,

it is likely that nursing practices contribute significantly to the differences between these groups, with the greatest abuse being in prolonging the administration of narcotics beyond the second postoperative day.

It is generally assumed that patients who are quiet, resting, or sleeping are free of pain. Of approximately 500 doses of morphine administered for pain, 77.5 per cent of the doses which resulted in pain relief were associated with sleep at the time the patient was interviewed. However, when pain relief did not follow the morphine, 31.7 per cent of all unrelieved patients were also seemingly asleep at the time of the interview. When roused, they complained of pain. The relationship between sleep and pain relief, while generally true, does not always hold.

New Approaches in Treatment of Postoperative Pain.—A recent innovation in the treatment of postoperative pain has been the periodic installation of local anesthetics into the surgical wound by small indwelling catheters.[29] This has been reported to abolish the need for narcotics postoperatively. Undoubtedly, such therapy would prevent pain arising from the operative site, but would probably not affect the associated intestinal discomfort and other complaints of these patients. In addition, this technique may possibly increase the incidence of postoperative wound infections.

With the appearance of nalorphine, a morphine antagonist, it was hoped that combinations of morphine together with its antagonist would result in preservation of analgesia, but abolition of at least such side actions as respiratory depression. This has been tried by several investigators.[30] In all studies in which respiratory depression and other side actions have been adequately measured, no decrease in side-action liability has been found. Indeed, under some circumstances this combination of drugs resulted in more profound respiratory depression and sedation.

Another new approach has been possible since the introduction of chlorpromazine, which is known to potentiate the effects of analgesics, hynotics, and anesthetics. It has been used in the treatment of pain of cancer which has become refractory to the usual narcotics in large dosage.[31] The administration of chlorpromazine together with an analgesic enables pain relief to be achieved with smaller doses of narcotics. In addition, it has been reported that chlorpromazine itself is an anxiety-relieving drug. However, to date no data are available as to how much analgesia is potentiated and how much the side actions of narcotics are also potentiated. One would expect that at least the incidence of nausea and vomiting would be decreased by such a combination, since chlorpromazine is an effective antiemetic.

SUMMARY

An attempt has been made to collect the large amount of new information which has become available in the past ten years concerning postoperative pain, its characteristics, its use for research, and its treatment. With a better understanding of the postoperative patient, it is hoped that an improved treatment of this common and neglected painful state will result. Part of this improvement awaits the discovery of an ideal analgesic drug, and this challenge remains. The rest of the improvement awaits the intelligent use of available drugs, good nursing care, and a consideration of the psychologic needs of the patients.

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CONTROL OF PAIN IN METASTATIC CANCER

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INTRODUCTION

MALIGNANT tumors cause much of the severe pain which the practicing physician is called upon to relieve. Nearly every type of pain receptor may be stimulated during the months or years intervening between onset of the tumor and final death of the patient, so that the therapeutic resources of the physician may be taxed to the limit. Nevertheless, these pain problems are seldom entirely intractable. Some of the most effective medical approaches to this problem within the author's experience will be considered in this communication.

The first positive step taken in relief of cancer pain occurs when a physician indicates his willingness to assume responsibility for day-by-day care of the patient, and plans a logical therapeutic program which can be explained in simple, understandable terms to the patient to enlist his trust and cooperation. Many observers have noted the potentiating effect of anxiety and apprehension upon pain and pain thresholds.[1] Cancer pain is often most unbearable because hope, understanding, and personal interest have been withheld, consciously or unconsciously, from the patient by his physician or nursing attendants. The pitfalls in cancer care resulting from the physician's attitude toward this disease have previously been emphasized.[2] An aura of deliberate ignorance or misinformation as to their condition, which is enforced upon many patients by their physician, does not allay anxiety nor enhance faith in the doctor, and will seldom fool the more intelligent. The mechanism of recurrent severe pain in most cases should be explained in layman's language to the patient, without mentioning the underlying etiology unless specifically asked (and that will be seldom), so that the patient will understand that "pressure upon nerves," "bowel obstruction by adhesions," or "arthritis" is causing his symptoms. It is a wise policy to

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keep close to the actual truth as to the mechanism of pain production in order to avoid confusion in patient instruction and to create a solid background for use of more radical medical, surgical, or neurosurgical methods of pain control, should the need arise later.

Component factors involved in production of pain must be broken down next into various etiologic categories so that appropriate steps can be taken to attack individual pain mechanisms (Table I). Antibiotic therapy may reduce the pain of infected superficial tumors, while minimal surgical intervention such as the removal of a constricting primary bowel lesion, or the nailing or plating of a pathologic fracture resulting from an isolated osteolytic metastasis, may do more than any drug to control pain of mechanical etiology. On the other hand, the biochemical effects of metastases upon surrounding normal tissues can be minimized only by inhibiting tumor growth by means of ionizing radiation, radiomimetic agents such as nitrogen mustards, or by hormonal therapy. There has been as yet relatively little clinical exploitation of a multiphasic approach to pain control in neoplastic disease through controlling these individual mechanisms of pain production by well-chosen combinations of therapeutic agents, which may be more effective in the long run than alteration of the response of the patient to pain by narcotic drugs.

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TABLE I. SOME MECHANISMS OF CANCER PAIN PRODUCTION

A. Mechanical	
	1. Obstruction in hollow viscus with smooth muscle spasm
	2. Pathologic fracture
	3. Extrinsic pressure on bone or viscera
	4. Capsular distention
	5. Infiltration of perineural lymphatics
	6. Increased intracranial pressure
B. Inflammatory	
	1. Ulceration and/or necrosis
	2. Secondary infection
	3. Stromal reaction to metastasis
C. Vascular	
	1. Thrombophlebitis
	2. Tissue anoxia
D. Biochemical	
	1. Lactic acidosis adjacent to metastases
	2. Proteolysis by metastases

From the standpoint of antitumor therapy, it is hopeful to note that an increasing variety of cancers appear partly dependent upon constitutional factors for metastatic proliferation. These neoplasms can be inhibited for periods of months to years by appropriate hormonal therapy or chemotherapy. The growing list of human neoplasms which do not appear wholly autonomous include some carcinomas of the breast, thyroid, endometrium, bladder, prostate,

ovary, salivary gland, kidney, and some of the better-differentiated lymphomas and leukemias. Pain control in patients with these neoplasms should be regarded primarily as a problem of tumor chemotherapy, since long pain-free intervals can occur when the neoplastic disease is in remission. A fortunate side effect of hormonal therapy with adrenocortical steroids or sex hormones is the favorable psychotherapeutic effect, resulting in increased appetite, ambition, and *joie de vivre*, which aids greatly in long-term case management. In our Tumor Clinic, patients receiving hormonal therapy seldom require narcotic drugs in frequent or large doses.

TREATMENT OF MECHANICAL FACTORS CONTRIBUTING TO PAIN

Relief of bowel obstruction and control of blood loss by palliative resection of primary adenocarcinomas of the intestinal tract, even though hepatic metastases are present, will contribute to the comfort and longevity of the patient in many instances. Laparotomy with palliative resection of as much disseminated ovarian cancer as possible will permit radiation therapy or radiomimetic chemotherapeutic agents to be most effective and may postpone subsequent bowel or bladder disorders in these patients. Palliative resection of selected primary bronchogenic cancers also may be used as a prophylactic measure, since removal of bronchostenotic lesions and atelectatic suppurating lung will minimize subsequent pain in many patients. There is no drug substitute for intubation and continuous suction in the relief of cramping pain resulting from spasmodic bowel activity in chronic gastrointestinal obstruction by metastases.

One of the most important areas of pain prevention in cancer lies in the early recognition and prophylactic roentgen irradiation of osseous metastases, especially in weight-bearing bones. It is widely accepted that a major physiologic factor contributing to bone strength, in addition to vitamins C and D, minerals, proteins, and anabolic steroids, is the stress and strain of daily activity, which in some manner controls osteoblastic activity and modifies bone architecture.[3] Osteolytic bone metastases seldom respond to roentgen or other therapy, if the patient is confined to bed. Even in normal individuals, confinement to bed results in rapid demineralization and hypercalcuria.[4] Pathologic fractures of vertebrae resulting in cord compression and paraplegia, or fractures of the femora necessitating recumbent therapy usually convert an otherwise favorable case for palliative therapy into an intractable problem requiring the ultimate in nursing care. Therefore, patients with prior therapy for prostatic, mammary, thyroid, renal, or other types of bone-seeking cancer should have careful roentgen study of the spine and extremities every six to twelve months, or as soon as any unusual pain becomes manifest.

Diffuse osseous metastases may be present for some time with but little distortion of bone trabeculae. Pain may also result from perineural radicular involvement (especially in prostate and breast cancer) without osseous involvement detectable by x-ray. Dramatic pain relief may be obtained in both groups of patients by 2,000 to 4,000 r, or more, 250 kv. radiotherapy to the area from which the pain is radiating. Even advanced osteolytic metastases can often be inactivated by local x-ray therapy to the extent that pathologic fracture will not result. In severe osteolytic vertebral involvement, temporary recumbent

therapy with appropriate splinting by means of collars or casts may be necessary if cord damage is imminent. As soon as possible (usually within three to six weeks), gradual ambulation should be started within the local-pain tolerance of the patient, so that gravity-stress factors may assist in restoring some degree of normal bone structure. At times it is justified to take calculated risks with continued ambulation of patients during treatment, so important is upright position for maintenance of integrity of uninvolved bone and repair of diseased bone.

Hormonal therapy of metastatic breast, prostate, and ovarian cancer with osteolytic involvement is a most important adjunct to local x-radiation because of the tumor suppression resulting therefrom and the anabolic action of sex hormones upon the protein matrix of bone. In a case of biopsy-proved ovarian metastases to the lumbar vertebrae with paraplegia, x-ray therapy alone failed to arrest disease, which relapsed after 2,000 r of local therapy. An additional 2,200 r, administered with 150 mg. testosterone propionate weekly and 10 mg. stilbestrol daily (to inhibit possible gonadotropin stimulation of tumor growth) resulted in partial regression of neurologic signs and early recalcification in the area. In the care of chronic osteolytic bone metastases, when positive calcium balance has resulted from therapy (as shown by negative urine Sulkowitch tests), supplementary vitamin D and calcium lactate may be administered. Supplementary calcium therapy is not indicated when urine Sulkowitch tests are strongly positive for calcium, and may be hazardous. In one of our patients with very extensive mammary osteolytic metastases with an excellent remission after cortisone-thyroid therapy, negative urine Sulkowitch tests for calcium were noted consistently during an eight-month period on an unrestricted diet with 1.5 Gm. of added calcium lactate and 5,000 units of vitamin D. Symptomatic relief of bone pain was complete in this period, pathologic fractures in the pelvis healed, and recalcification of osteolytic lesions in skull, pelvis, and femora occurred.

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REDUCTION OF INFLAMMATORY COMPLICATIONS

Primary cancers of the oropharynx and vulva are especially apt to be initially painful as a result of the local mixed bacterial infection associated with these lesions. Antibiotic therapy usually provides only transient pain relief, even when cultures and sensitivity studies are utilized as a guide for selection of the most appropriate antibiotic agent. Local roentgen irradiation may give more prolonged pain relief, especially if the primary tumor site receives an adequate cancerocidal dose (6,000 to 8,000 r), so that epithelial integrity may ultimately be re-established. Supervoltage irradiation may be of assistance in controlling pain from deep-seated primary tumor sources such as esophageal and pancreatic carcinoma.

The anti-inflammatory activity of cortisone and various corticoid derivatives can be useful in palliation of pain in some patients, perhaps as a result of reduction of the desmoplastic reaction associated with neoplastic invasion. Generally, maintenance dosage must be on the high side, sufficient to produce signs of hypercorticism, if any degree of palliation is to be anticipated. As a rule, this means maintenance doses of cortisone, ranging from 100 to 300 mg.; or of delta-1 cortisone (Meticorten) ranging from 20 mg. up. Continued use of these compounds

at this dosage level carries a definite risk of increasing the rate of metastatic growth, but this is not a contraindication for their use if they are effective in controlling symptoms referable to advanced cancer.

It is always wise to prevent inflammatory complications, if possible, in palliation of advanced cancer. Pneumonectomy may prevent numerous local complications, including pain, in disseminated bronchogenic carcinoma. Simple mastectomy may prevent pain resulting from ulceration of the primary tumor in advanced breast cancer, and removal of obstructive primary neoplasms in the gastrointestinal tract has already been mentioned. Sound surgical judgment must be used with caution to avoid extensive surgery in tissues heavily infiltrated with metastases, which can be disastrous.

CONTROL OF PAIN OF VASCULAR ORIGIN

Arteries are highly immune to neoplastic invasion, and therefore tissue anoxia from arterial insufficiency is seldom a pain mechanism requiring therapy. This is not so, however, with veins, which are frequently invaded by malignant tumors, resulting in thrombosis. Advanced cancer also induces a number of circulatory changes including venous stasis, platelet embolism, increased erythrocyte sedimentation, hyperglobulinemia, changes in the permeability of arterioles, venules, and capillaries, and alterations of endothelium of the smallest blood vessels, resulting in increased adhesiveness for leukocytes and platelets.[5] These multiple factors predispose to thrombophlebitis, especially in some pancreatic cancers where multiple episodes of thrombophlebitis are known to occur among the earliest disease manifestations. In rare instances, such as cancer of the body and tail of the pancreas, without obstructive jaundice or massive liver metastasis interfering with normal prothrombin synthesis, heparin or Dicumarol therapy may be helpful in controlling painful episodes of thrombophlebitis.

CONTROL OF PAIN REFERABLE TO CANCER METASTASES PER SE

After careful review of other possible pain etiologic factors, there remains the major problem of pain directly referable to the invasive activity of the primary cancer or its metastases. Involvement of pleura and peritoneum by metastasis, with production of either septic or aseptic pleuritis or peritonitis and resultant adhesions, results in one of the most distressing terminal disorders in cancer. Rapid hepatic distention by metastasis produces considerable pain, with diaphragmatic and peritoneal components, if there is superficial inflammatory reaction as a result of necrosis or local metastatic invasion. Bone pain may develop as a result of periosteal disturbance by metastasis. In general, control of pain resulting from these local aspects of cancer growth is a biochemical problem, since one must attempt (1) to reduce the rate of abnormal cell growth and (2) to reduce the irritative properties of cancer cells upon adjacent tissues as a result of lactic acid production, proteolytic enzyme production, and mechanical pressure.

Ingestion of alcohol can produce severe pain from metastatic lymphoma, and hence should be avoided in these patients.[6] Local administration of radioactive gold or nitrogen mustard has been effective in controlling pleural and

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peritoneal effusions and pain therefrom, in some instances.[7,8] The local use of these substances is ineffective and may offer considerable hazard when adhesions have formed with compartmentation of the effusion. In many instances, the pleural or peritoneal fluid is the result of soft-tissue invasion and lymphatic involvement well beyond the very limited (2 mm.) beta irradiation of Au^{198}. Local deep roentgen irradiation, therefore, may be more helpful in control of local tumor masses causing pain, while diffuse pulmonary metastases from bronchogenic, renal, or breast cancer associated with pleural pains and effusions may be best treated by intravenous nitrogen mustards plus corticoids, or other systemically active agents.

Nonspecific Anticancer Therapy.—In the case of widely disseminated pulmonary or hepatic metastases, systemic chemotherapy using intravenous nitrogen mustard, combined with hormonal therapy using ACTH or cortisone, has, in our experience, been the most effective method of temporarily inactivating cancer growth and pain therefrom, without serious hazard to, or increased hospitalization of, the nearly terminal patient.[9] Adrenocortical steroids supplement the lympholytic action of nitrogen mustards and may have a protective action upon the blood-forming organs, reducing toxicity. Patients with diffuse cancers of the breast and prostate should have had the gonads surgically removed or have been on effective antigonadotropin therapy and received maintenance doses of 100 mg. daily of cortisone for a few days before and during mustard treatment. Other patients with metastases from pulmonary, pancreatic, gastric, or colon carcinomas should receive 20 to 40 units of ACTH gel twice daily for a few days before and during mustard treatment. Disseminated cancers from testicular and ovarian sources should receive antigonadotropin therapy in the form of androgens or estrogens during therapy. Steroid therapy is tapered down after the last dose of mustard. Nitrogen mustard, dissolved only seconds before injection into a rapidly running intravenous solution of 5 per cent glucose and water, should be administered in 3 injections at forty-eight-hour intervals, giving 0.2 mg. per kilogram of body weight at each dose. Barbiturates and chlorpromazine (Thorazine, 50 to 75 mg.) immediately prior to mustard therapy aid in controlling nausea. The third injection should be withheld from patients with extensive previous radiation therapy, and those with granulocytopenia under 50 per cent, or leukopenia below 5,000 per cubic millimeter. No mustards should be given in cases where pancytopenia exists, with leukopenia below 3,500 per cubic millimeter, platelet deficiency under 50,000 to 100,000 per cubic millimeter, or clinical purpura, since like other nonspecific agents they are highly toxic to normal rapidly regenerating tissues such as red bone marrow. In cases of extensive osseous metastases or prior x-radiation with leukopenia or pancytopenia, sternal or iliac marrow aspiration should be carried out to evaluate the degree of bone marrow damage prior to administration of nitrogen mustards or similar cytotoxic agents such as triethylenemelamine. Pulmonary and hepatic metastases originating from mammary, renal, gastric, and colonic carcinomas have responded objectively to combined steroid-nitrogen mustard therapy for periods of two to six months in some instances.

Multiple myeloma offers one of the most serious problems of pain control, and no adequate chemotherapeutic agent has yet been developed which is valu-

TABLE II. SPECIFIC ANTITUMOR (HORMONAL) THERAPY

ORIGIN OF CANCER	HORMONAL STIMULUS		HORMONAL THERAPY		
	INDIRECT	DIRECT	TYPE OF AGENT	PREPARATION	DOSE SUGGESTED
Prostate	Pituitary gonadotropins	Testosterone androsterone and other androgenic steroids (chiefly from testis)	Surgical castration; and/or antagonists to androgens or gonadotropins	Stilbestrol Tace Ethinyl estradiol	5-15 mg./day 8-16 mg./day 0.5-1.5 mg./day
Breast and Endometrium	Pituitary gonadotropins	Estrogens of uncertain structure, from ovarian and adrenocortical sources	For patients over 60-65, antigonadotropins	Synthetic estrogens such as Stilbestrol	(See above)
	Adrenocorticotropin (?)		Any age group: Estrogen antagonists (also act as antigonadotropins)	Testosterone propionate Methyl testosterone	150-300 mg./wk. 30-100 mg./day
			Any age group: Anticorticotropin (plus surgical castration for those under 65 years of age)	Cortisone Hydrocortisone Meticorten (plus dessicated thyroid as synergist)	100 mg./day 80 mg./day 15-20 mg./day 30-120 mg./day
			Under 65 years: Hypophysectomy or oophorectomy plus adrenalectomy	Substitution therapy with cortisone or derivatives	Cortisone 50 mg./day
Ovary	Thyroxin (?) Estrogens (?)	Pituitary gonadotropins	Antigonadotropins; surgical castration	Testosterone propionate or Stilbestrol (singly or in combination)	200-300 mg./wk. 10-15 mg./day
Thyroid	Iodine deficiency; thyroid insufficiency	Pituitary thyrotropin	Thyroid hormone	Dessicated thyroid (plus cortisone as synergist)	60-240 mg./day 50-100 mg./day
Salivary glands		? Thyrotropin ? gonadotropins corticoids	Estrogens	Stilbestrol	15 mg./day
Kidney	Growth, adrenocortical hormones, androgenic steroids	? renal factor	Removal of primary tumor and anticorticotropin therapy	Cortisone or derivatives	(See above)

able for most patients. Urethane in two to five Gm. daily doses (enteric-coated capsules) is of symptomatic benefit, at the price of nausea and anorexia, in at least one-half of the cases. Stilbamidine benefits occasional patients but requires daily intravenous injections and has neuropathic and nephrotoxic potentialities

which are less likely with 2-hydroxystilbamidine.[10] ACTH or cortisone may palliate some patients and may be utilized along with local x-radiation, which is still the most popular agent for control of locally painful lesions.

Gout may be observed as a complication of chemotherapy which results in excessive destruction of tumor tissue. In some instances, gout develops spontaneously with extremely rapid nucleic acid synthesis and catabolism, as in the more acute phases of leukemia. Tissue urate deposition secondary to hyperuricemia and urinary lithiasis may be prevented by adequate fluid administration to ensure urinary output above 1,500 to 2,000 c.c., possibly with six to eight Gm. added sodium bicarbonate orally, when this hazard is recognized. Uricosuric agents such as probenicid (Benemid) are often contraindicated in the acute phases of this type of hyperuricemia, but may be utilized in the treatment of secondary gout of chronic duration, such as may accompany myeloid metaplasia or chronic leukemia.[11] Reduction of blood uric acid levels in the latter group of patients may control some of the manifestations of painful joints.

Specific Antitumor Therapy.—Semiautonomous metastases from mammary, prostatic, renal, thyroid, endometrial, and ovarian sources will often respond to hormone therapy directed at inhibition of the specific endocrine stimulus to tumor growth.[12] Table II summarizes the rationale and dosage of hormones commonly used in our clinic. Although it is often best to utilize all antitumor agents serially to derive maximum information about the response to each form of treatment and to extend the duration of response as much as possible, remission may be achieved only by combination treatment in cases with fulminating metastasis. This is particularly true of pulmonary, cerebral, and hepatic involvement.

In metastatic breast and prostate cancer, controlled for one or more years by sex hormone therapy, relapse may take place in some instances when the tumor develops an acquired tolerance for the agent used. When re-exacerbation of symptoms referable to the neoplasm takes place under these circumstances, one should first withdraw the hormonal agent used, which may of itself lead to a second remission of pain. Subsequently, an alternative method of treatment may be utilized, which, in our opinion, is most apt to be successful when it is based upon an attempt to destroy or inhibit endogenous sex hormone production. This can be approached by hypophysectomy, gonadectomy plus total adrenalectomy, or gonadectomy plus cortisone in moderate doses.

Gonadectomy (if not already carried out), followed by cortisone administration in 50 to 100 mg. maintenance doses, is often the most practical solution to this problem of relapse of breast cancer after remissions induced by sex hormone therapy, presumably largely because it is effective in reducing adrenocortical as well as gonadal sources of sex hormones. X-radiation of the ovaries is not reliable in preventing further sex hormone secretion, especially in younger women. In prostatic cancer relapsing after orchiectomy and/or estrogen therapy, cortisone or delta-1-cortisone (Meticorten) in low doses occasionally controls bone pain from metastases. Objective osseous repair and prolonged survival (over one year) seldom occur, possibly because cortisone therapy has a mild enhancing effect upon androgenic hormone production in castrates.[13] Cortisone also is

partly metabolized to androgens prior to excretion, which may likewise interfere with its antitumor action in prostatic cancer. No evidence exists for conversion of cortisone to estrogenic derivatives. Cortisone therapy in castrate females markedly reduces estrogen production so that persistent hot flashes reappear in most cases with prior oophorectomy, and temporary remission occurs in about two-thirds of advanced mammary cancer patients to whom it is administered.[14] Dessicated thyroid in 15 to 120 mg. doses has been of definite value as a synergist with cortisone in controlling pain from osseous metastases of breast cancer, as well as in reducing urinary calcium excretion and suppressing abnormally high copper-resistant serum acid phosphatase activity. Administration of thyroid probably indirectly contributes also to generalized recalcification and repair of metastases, which have been noted in the majority of patients whose remissions exceed six months.[15] It may be pertinent in this connection that two-thirds of breast cancer patients at autopsy show evidence of abnormal thyrotropic activity,[16] even though thyroid function studies in our experience are usually normal.

Thus far, the reported duration and type of benefits resulting from surgical hypophysectomy and total adrenalectomy do not differ significantly from experience obtained in our clinic with medical inhibition of the pituitary and adrenals, using cortisone and thyroid hormone therapy in functionally castrate patients. Recalcification of osseous lesions appears as frequently after cortisone-thyroid therapy as after total adrenalectomy[17] or hypophysectomy.[18] Women over 70 need not undergo oophorectomy to be functionally castrate, so that excellent remissions may be obtained using cortisone alone in some of the poorest operative risks among the elderly. Surgical interference with hypophyseal or adrenocortical function in breast cancer seldom palliates those who have failed to respond to gonadectomy, to male or female sex hormones, or cortisone plus castration therapy. There is pathologic evidence of adrenocortical hyperplasia in some of these patients[16] which may not respond even to high dosage cortisone therapy and which may serve as a source of "tumor-tropic" steroids. The possible benefits of operation must be balanced against risks, expense, and added morbidity to be anticipated.

Potentiation of X-radiation by Specific Antitumor (Hormonal) Therapy.—When successful, hormonal therapy is more often carcinostatic than carcinolytic. To obtain maximum results, especially in osseous, pulmonary, and hepatic metastases, supplementary carcinolytic therapy is often necessary. Local x-radiation or systemic ionizing agents, such as nitrogen mustards intravenously or triethylenemelamine by mouth, can be used, depending upon the location of the major metastases in lung or gastrointestinal tract, respectively. Although some hormones alter the action of ionizing radiation,[19] the general principle seems not to have been clearly recognized that neoplasms growing under the influence of an urgent hormonal stimulus will be less radiosensitive than in the absence of such a stimulus. Our own experience in metastases from thyroid, ovarian, prostatic, renal cell, and mammary carcinoma, and malignant melanoma, has been in accord with this observation. For instance, one of two patients with metastatic thyroid carcinoma, otherwise identical in age, location of principal metastasis, and highly undifferentiated type of cancer, was treated with cortisone

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and thyroid in doses sufficient to inhibit thyrotropic function before, during, and after x-ray therapy. Both cases were treated by the same radiologist using the same equipment at the same time with approximately equal doses. The patient without thyrotropin suppression died within three months of fulminating local recurrence, while the other patient died fifteen months later of deep cervical invasion, without local recurrence. Recently, estrogen administration has been observed to improve results of radiation therapy in salivary gland neoplasms.[20]

SUPPRESSION OF PAIN APPRECIATION BY NARCOTICS, ANALGESIC AGENTS, AND SEDATIVES

The discussion of these agents has been deferred until last, because other means of controlling cancer pain should be fully utilized before narcotic agents are required. Three interrelated groups of symptoms which contribute to the cancer patient's disease are those of anxiety, nausea or anorexia, and pain. Often these occur simultaneously and each may contribute to the other. The food aversion is not related necessarily to gastrointestinal obstruction or hepatic metastases, and may result in abnormally-timed appetite urges.

Daily rounds at the patient's bedside, barbiturates, or Rauwolfia derivatives are helpful in allaying anxiety. Chlorpromazine in 25 mg. doses may also be helpful and will control some of the nausea and anorexia, which may also remit if hormone or chemotherapeutic-induced tumor regression occurs. Use of some of the newer tranquilizing agents such as meprobamate (Miltown) may be considered. Salicylates and codeine suffice for many patients with mild pain of osseous origin. Other oral therapy of value for pain not responding to milder medication consists of methadone (10 to 15 mg. every 6 hours orally), Pantopon (10 to 20 mg. intrabuccally every 4 to 6 hours), levorphan (Levo-Dromoran) (2 mg. every 6 hours orally), or metopon (3 mg. every 6 hours orally). The last two synthetic morphine analogues are more effective than morphine in controlling experimentally produced pain. Meperidine (Demerol) has been infrequently used in our Clinic because of its addicting potentialities,[21] resulting in early development of large requirements and inadequate pain relief in some patients. The spasmolytic properties of meperidine, however, may be of great value in controlling pain from gastrointestinal lesions.

For parenteral use, repeated injections of methadone or nocemorphan (Dromoran) are less traumatic than meperidine, since they can be administered subcutaneously without irritation. Methadone or levorphan have been our agents of choice in the more severe pain problems also, because tolerance development is less rapid and they are less conducive to obstipation than morphine.[22] Morphine, dihydromorphinone (Dilaudid), or Pantopon have been utilized when apprehension and alarm accompanied pain, in the very last stages of malignant growth. Recently development of a new antagonist blocking morphine-induced respiratory depression has permitted administration of 120 to 180 mg. of morphine at a dose for pain control.[23] Nalorphine is now generally available to block undue side effects or overdosage with morphine and its natural or synthetic analogues in 10 to 15 mg. dosage.

Neurosurgical procedures are valuable in rare selected cases of chronic intractable cancer pain and should be carried out before narcotic tolerance and requirement is excessive. Adequate combination treatment of the neoplasm, using hormones, radiation, and chemotherapy, coupled with judicious selection of sedatives and narcotics, obviate the need for neurosurgery in most patients and prevent undue suffering from many cancers in the end stages.

SUMMARY

A multiphasic approach to cancer pain control is outlined, utilizing prophylactic palliative surgery or x-ray therapy when necessary. Hormone therapy acts synergistically with local irradiation or systemic radiomimetic agents for pain relief from breast, prostate, thyroid, and ovarian neoplasms. Synthetic morphine derivatives often adequately control pain without development of excessive requirements until near the patient's death. Morphine or other opiates remain the best agents for terminal care in cases which have not become tolerant by premature resort to these drugs.

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THE ANESTHESIOLOGIST AND THE MANAGEMENT OF PAIN

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THE physician anesthetist occupies most of his time supervising the comfort and safety of patients during operative procedures. In the performance of these duties, he employs general anesthetics, regional, local and topical anesthetics, muscle relaxants, analgesics, sedatives, and, occasionally, hypnosis. His constant use of these agents and methods usually qualifies him to be a source of information for other physicians less familiar with them. It was a matter of natural evolution for anesthesiologists to concern themselves with nonsurgical pain problems. The teaching residencies in anesthesiology have expanded this interest by providing moderate to extensive training in diagnostic and therapeutic nerve blocks, and in many instances by the formation of pain clinics.

It should be clear, however, that such experience and training does not constitute a claim that every anesthesiologist, or even the majority of them, are to be regarded as specialists in the treatment of pain. Any physician, regardless of his specialty, may by virtue of interest, study, and patient care style himself a pain specialist. The anesthesiologist must evince similar interest and devote himself to the study and care of patients in pain before he can lay claim to such a title.

The nature of many of the problems presented by patients complaining of pain excludes the average anesthesiologist from contributing more than technical skill to the treatment of pain. Except for certain acutely painful conditions, most patients with complaints of pain, particularly those with chronic, persistent, or intractable pain, require infinite time from the physician for careful and systematic study, questioning, and examination. In view of the seemingly ever-increasing length of surgical schedules and the real shortage of physicians practicing anesthesiology, the time available for most anesthesiologists to devote themselves to patients with pain problems is minimal. In teaching institutions or in group practice where a large number of anesthesiologists work together, it is possible for individuals interested in the problems of pain to devote a major portion of their time to this interest. Such clinics or such interests are likely to be uncommon rather than the rule.

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In consultation with other physicians, however, the anesthesiologist may contribute significantly to the patient's welfare by helping to discover the etiology of painful conditions, assist in the actual treatment of processes producing pain, or effect temporary to permanent relief of the pain by regional blocks. The following paragraphs will attempt to familiarize the internist and general practitioner with the areas in which practically every anesthesiologist can make contributions to the diagnosis and treatment of patients in pain.

Spinal Block.—The injection of local anesthetic solutions into the intrathecal space can assist in the diagnosis and treatment of certain types of pain below the upper extremities. In the presence of chronic and persistent pain arising within the abdomen, from the abdominal wall, pelvis, or lower extremities, the failure of a spinal block to produce relief of pain may be a highly significant factor. However, in the case of abdominal pain, the failure of intrathecal local anesthetics to produce pain relief does not automatically suggest that the patient is suffering from pain of cranial origin or of psychoneurosis. The sensation of pain appears to be transmitted over extraspinal pathways under certain circumstances. It may be impossible to block these completely with spinal anesthesia even though the level of sensory anesthesia may reach to the clavicles.

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Determination of the level of sensory anesthesia needed to produce pain relief may provide worth-while information to the neurosurgeon contemplating chordotomy. The use of differential spinal block (injection of 0.2 per cent procaine) in order to provide sensory and sympathetic block without interference with motor function may enable the diagnosis of intestinal dyskinesia to be made.[1] Often, the performance of a spinal block early in the study of a patient in pain will save valuable time by eliminating the need for attempts at relief of pain with peripheral nerve blocks.

Most of the common local anesthetic agents have been injected to produce spinal anesthesia. For diagnostic spinal blocks, procaine is usually the agent of choice. To produce more permanent block, the intrathecal injection of solutions containing ammonium sulfate has been advocated for the treatment of certain types of pain.[2] However, this technique has failed in most hands. Absolute alcohol has been injected into the subarachnoid space for the relief of intractable pain of carcinoma. This is a major procedure and carries with it the same threat of loss of motor function or of control of bladder or bowel as does a chordotomy. Certain types of pain associated with terminal carcinoma, however, may be effectively treated by this method.[3]

Epidural Nerve Blocks.—Effective block of peripheral nerves can be obtained by injecting local anesthetic solutions into the epidural space either by way of the caudal canal or at any site along the vertebral column. Block can be obtained either by the single injection technique or by the insertion of a catheter into the epidural space with the subsequent intermittent injection of local anesthetic solutions. The spread of solutions within this potential space is not entirely controllable, but with experience an anesthesiologist can predict with reasonable accuracy the extent of sensory anesthesia that will result from his injection. In the catheter technique, often the block provided by the initial injection exceeds that resulting from subsequent injections, and, not infrequently, repeated in-

jections fail to provide satisfactory block. The potential hazard of catheters in situ for long periods of time is not to be ignored, nor is the possibility of neuritis or neural damage from the catheter lying in close proximity to nerves.

In the diagnosis or treatment of painful conditions of the thorax or abdomen, it is often technically simpler to perform an epidural block with a single needle than it is to do multiple paravertebral nerve blocks. It may also be more reliable and less painful to the patient. In the treatment of either acute or chronic vasospastic disease of the lower extremity or of arterial occlusion up to and including the bifurcation of the aorta, epidural block may provide significant pain relief as well as lead to an improvement of the peripheral circulation. Occasionally, the apparent need for amputation of a lower extremity may disappear.

Under most circumstances, procaine or other commonly used local anesthetics are injected into the epidural space. Destructive solutions are not generally employed, although techniques describing the use of epidural alcohol for the treatment of intractable pain have appeared.[4] Studies have indicated conclusively that even though an anesthetic solution is injected into the epidural space, a significant percentage of the drug appears in the cerebrospinal fluid.[5] Epidural catheters, inserted in the treatment of vasospastic disease, have been left in situ for many days.[6] By means of catheters, either an intermittent injection of local anesthetic can be performed or the solution can be administered by a continuous drip method.[3]

Regional Block of Peripheral Nerves.—Regional block of peripheral somatic nerves is most effective in acute or subacute painful conditions.[7] It has proved worth while in the treatment of fractured ribs,[8] costochondral separation, brachial neuralgia, acute and subacute bursitis, greater occipital neuralgia, and in myospastic disease when the spasm is confined to muscles supplied by one or two nerves accessible to the blocking needle. By means of blocks of peripheral nerves, it is often possible to differentiate the site of origin of pain. For instance, a block of intercostal nerves may permit a differentiation of pain arising in the thoracic or abdominal wall from that arising within the thorax or abdomen. It is possible to block almost any nerve trunk within the body that can be reached with a needle.

The main drawback to blocks of peripheral nerves is the lack of a reliable, long-lasting anesthetic agent. All of the available local anesthetics produce anesthesia lasting a few hours. Often the effects of a procaine nerve block will long outlast the duration of the actual sensory anesthesia produced by the procaine, but in chronic painful conditions the relief afforded by the block is most often limited to the duration of sensory anesthesia. Thus, while complete relief may be afforded for several hours, patients usually despair of the need for repeated procedures. Numerous drugs combined with oils or other substances designed to prolong the duration of local anesthesia have been introduced, but none has withstood the test of time, and some have their own inherent hazards.[9] Alcohol or phenol has been advised for permanent or semipermanent blocks. The former is used in concentrations ranging from 50 per cent to absolute alcohol. Its use is associated with a high incidence of postinjection neuritis. Alcohol has been particularly effective for blocking the fifth cranial nerve or its branches in the

treatment of tic douloureux. Phenol has been used for blocking peripheral nerves in 6 to 10 per cent aqueous solutions. It produces less neuritis but also appears to be less effective than alcohol.

Blocks of Autonomic Nerves.—The cervical sympathetic chain, the stellate ganglion, and the lumbar paravertebral sympathetic chain are reasonably accessible and can be effectively blocked with local anesthetic or destructive agents. Blocks of the thoracic sympathetics can also be accomplished, but are more hazardous. Blocks of the paravertebral sympathetic nerves are usually performed for occlusive vascular disease or causalgia. Usually an effective block is demonstrable by the increased warmth of the part and a local anhydrosis. Signs of an effective block of the thoracic sympathetics are less definable and may only be apparent by relief of visceral types of pain. These nerves have been anesthetized or destroyed for the relief of various types of chest pain including cardiac pain, but the reported risk has been high.[10] Block of the stellate ganglion or cervical sympathetic chain is usually apparent from development of a homolateral Horner's syndrome. For awhile, a stellate ganglion or cervical sympathetic block was considered good treatment for cerebrovascular thrombosis or embolism, but the consensus now appears to be that little is accomplished by such procedures. A stellate ganglion block may prove of value in the treatment of Raynaud's disease, shoulder-hand syndrome, causalgia of the arm or hand, and occasionally in the relief of certain types of cardiac pain, or pain of malignancy of the neck.

Blocks of the celiac ganglion or of the splanchnic nerves frequently prove valuable. The relief of the pain of acute pancreatitis following the successful performance of a celiac ganglion block is often dramatic and considerably prolonged beyond the duration of action of the local anesthetic agent per se. Excellent and prolonged relief may be afforded the patient with carcinoma of the pancreas by a phenol block of the celiac ganglion.

Six to 10 per cent phenol appears almost to be a specific agent for prolonged or permanent blocks of the sympathetic ganglia.[11,12] It is equally as effective as alcohol, and less irritant.

Complications of Nerve Block.—All nerve blocks have inherent hazards.[13] These range in importance from a minor sensitivity reaction, to death. If epinephrine is used in the local anesthetic solution, the incidence of nervousness, palpitation, cool and moist skin, and feeling of faintness will be high. With blocks about the neck or chest, pneumothorax, vascular punctures, and epidural or intrathecal injections may occur. Regional blocks should not be employed if the patient is on anticogulant therapy.[14] The use of destructive agents may be followed by a disturbing peripheral neuritis more troublesome than the original complaint.

Infiltration Procedures.—Not infrequently, the infiltration of skin, subcutaneous or muscle tissue in or overlying painful areas will result in significant pain relief. Most susceptible to such procedures are muscle spasms or trigger areas.[15] Such measures are apt to be most successful if combined with psychotherapy, analgesics, and physical therapy. Painful scars of operations can often, but not always, be treated satisfactorily this way. When infiltration procedures

are undertaken, the local anesthetic should be in dilute solution, e.g., procaine 0.5 per cent.

Intravenous Local Anesthetics.—A considerable volume of literature dealing with the use of local anesthetics for the relief of pain has been accumulated. Many of the original claims of the value of intravenous procaine or tetracaine have not been substantiated, but nonetheless there are certain painful conditions in which these drugs may effect relief. Aching, visceral or vascular pain seems to be more responsive than acute somatic pain. An exhaustive study of the mechanism by which intravenous procaine produces pain relief has recently appeared.[16]

General Anesthesia.—Occasionally, the administration of a general anesthetic may help in the diagnosis or in the treatment of a painful condition. By the administration of a small amount of thiopental, the diagnosis of marked abdominal distention due to neurosis as described by Alvarez[17] can be established. A general anesthetic may be administered while an extremity is manipulated to break up painful adhesions within a joint cavity. A general anesthetic may assist in the determination of the degree of permanency of chronic spasticity and allow for a more intelligent planning of the future course of therapy. Thiopental in dilute solution intravenously has been used in conjunction with opiates in the control of pain in the terminal stages of malignancy or leukemia. Finally, trichlorethylene has been used successfully in the reduction of pain associated with malignant disease.[18] The latter can be self-administered by the patient.

Muscle Relaxants.—Curare preparations may find great utility in the treatment of painful muscle spasms associated with trauma, torticollis, and arthritis.[19] Several long-acting or depot relaxant drugs are available. Because of his daily use of these drugs, the anesthesiologist can offer advice as to dosage, complications, and the treatment of complications, should they arise. The administration of these drugs should always be under the supervision of an anesthesiologist.

The Treatment of Chronically Painful Conditions.—As mentioned previously, the anesthesiologist has no special claim to the title of pain specialist. This particularly applies to the treatment of chronically painful conditions. Unfortunately, patients falling into this category require painstaking questioning, examination, study, and prolonged treatment. Many specialists may be able to contribute to the welfare of these individuals, but seldom is any one specialist able to accomplish all that is required. Internists, neurologists, neurosurgeons, radiologists, psychiatrists, and physical therapists, as well as anesthesiologists, may have much to offer collectively, but each alone may contribute little to the patient's comfort. Some one of this group must be the organizer and the force ultimately responsible for the patient's care. If the anesthesiologist has a particular interest in this field, he may be that responsible physician; but lacking the time or interest to ferret out all the details that need investigating, he may be little more than another physician crossing the path of the patient's quest for relief. Multitudinous factors may underlie a patient's complaints of chronic pain. Failure to grapple with all factors dooms the attempted treatment. These are the prime reasons why nerve blocks alone fail in providing significant relief to patients with chronic pain. As one contributor of many to a planned attack

upon a single patient's problem, the anesthesiologist's contribution may be great. However, the anesthesiologist should not be looked upon as "a court of last resort" in regard to this contribution. His effort may be far more important early in the patient's treatment rather than later. This is especially true in such conditions as causalgia, postherpetic neuralgia, and painful phantom limb.

As has been true with other specialties of medicine, there are anesthesiologists who have made highly significant advances to our understanding of pain and its treatment. This has been particularly true within the last decade. New local anesthetics have been introduced and tested; simplification and popularization of regional nerve blocks has been widespread among the specialty[20-22]; inquiries into the action, effectiveness, and limitations of analgesics and sedatives have been made; investigations concerning the effect of drugs upon the intangibles of mood and mind have been published; diagnostic tests employing spinal anesthesia have been reported; researches into the sites of action of intravenously injected local anesthetics have been made; and a major reference work on pain has been published.[3] As a comparatively new specialty, anesthesiology can be proud of its already significant contributions to our knowledge and treatment of pain.

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ADDICTION PROBLEMS IN THE MEDICAL USE OF NARCOTIC ANALGESICS

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THE symptomatic relief of severe pain is possible by the use of the narcotic analgesics, a group of potent and specific drugs which are unsurpassed for this purpose.

Unfortunately, all currently available narcotics possess addiction liability. Once addiction has occurred, it is associated soon with seriously disrupting personal, social, and economic consequences. Narcotic addiction commonly is more disastrous for the patient, for the family unit, and for society than any persistent pain or distress for which the narcotics were prescribed initially. Therefore, the prevention of narcotic addiction is an imperative consideration in the use of narcotic analgesics in all cases, except those of painful terminal illness.

INCIDENCE OF ADDICTION DURING THERAPEUTIC ADMINISTRATION

While the Bureau of Narcotics has published estimates of the number of nonmedical narcotic addicts in the United States (now about 60,000),[1] the number of medical addicts under physicians' care is unknown. It is surmised that narcotic addiction develops infrequently under conditions of ordinary medical use, since, every year, many persons receive narcotic analgesics for short periods of time without becoming addicted.[2] In this sense, drug addiction appears to have a low "attack rate" when exposure to narcotics occurs during illness. This reasoning seems both valid and reassuring.

Nonetheless, study of narcotic addicts reveals a more somber picture. In 1925, Kolb[3] investigated a representative group of 230 opiate addicts and found that 14 per cent were "persons of normal nervous constitution" who had been addicted in the course of medical treatment. Pescor[4] reported that of 1,036 patients admitted to the U. S. Public Health Service Hospital at Lexington, Kentucky during 1937, 3.8 per cent were normal persons who had become addicted to morphine "given legitimately for the alleviation of a painful or destressing

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disease." Although these were psychiatric studies aimed at classifying the types of personality encountered among opiate addicts, the figures in these reports have often been taken to represent the incidence of narcotic addiction during medical treatment. Used in that manner, these figures must be low, since addiction to narcotics during therapeutic administration is surely not restricted to persons of normal personality structure. That these figures are low is borne out by the following investigations.

In 1933, Robinson and Johnson[5] reported that in 50 consecutive cases of morphine addiction encountered in their hospital practice, 56 per cent had first received narcotics from a physician. They estimated that 28 per cent of all opiate addiction in the country originated from physicians. In a more recent survey conducted by the author at the United States Public Health Service Hospital at Lexington, Kentucky,[6] it was found that 27 per cent of white patients and 1.2 per cent of Negro patients admitted during 1952 had become addicted to narcotics first prescribed for them by a physician in the course of treatment for illness. It was pointed out also that all patients addicted to synthetic narcotics—principally meperidine (Demerol)—had begun the use of the drugs as a result of therapeutic administration by physicians, and had depended on physicians for their supply of drugs. In a subsequent paper, Rasor and Crecraft[7] reported that the number of meperidine addicts at the Lexington hospital had risen from 6 per year in 1946 to 144 yearly between 1951 and 1953.

Other data obtained from the study of narcotic addicts suggest that drug addiction during medical use occurs in cases where it is avoidable. Robinson and Johnson[5] believed that 70 per cent of their 50 cases had been needlessly addicted. The author has shown that medical addicts treated at the Lexington hospital—a group which included individuals with essentially irreversible chronic illnesses—could be withdrawn readily from narcotics and the discomfort incident to their illness managed by other methods.[6] Rasor and Crecraft[7] felt that over one-half of their cases of meperidine addiction closely resembled medical addicts as defined by the present writer, both in regard to the onset of addiction and their course in the hospital after withdrawal of drugs.

DEFINITION OF NARCOTIC ADDICTION

The Expert Committee on Drugs Liable to Produce Addiction of the World Health Organization has defined drug addiction as ". . . a state of periodic or chronic intoxication detrimental to the individual and to society, produced by the consumption of a drug (natural or synthetic). Its characteristics include: (1) an overpowering desire or need to continue taking the drug and to obtain it by any means; (2) a tendency to increase the dose; a psychic (psychologic) and sometimes a physical dependence on the effects of the drug."[8]

For clinical purposes, drug addiction is best defined in terms of the problems with which the physician is called upon to deal, once addiction is established. In general, the problem involved is the management of persons who display pronounced disturbances in behavior when they are deprived of certain drugs whose abuse is considered to be harmful to the individual, to society, or both. In this sense, according to Wikler,[8] "drug addiction" is synonymous with "phar-

macological dependence," and is said to exist when abrupt and complete withdrawal of certain drugs is followed by an "abstinence syndrome." This abstinence syndrome may consist only of "craving" and persistent manipulative behavior directed at securing drugs. These abstinence phenomena are termed "purposive." They may occur alone or may be associated with more transitory "non-purposive" changes involving the neuromuscular, autonomic, and endocrine systems, which constitute the signs of abstinence from narcotics. This definition also outlines the changes the physician would aim to avoid in patients receiving narcotics.

ETIOLOGY OF NARCOTIC ADDICTION

The etiology of narcotic addiction is multifactorial. It results from the interaction, at least, of pharmacologic personal, and situational factors.

Pharmacologic Factors.—There are now five chemical classes of drugs that are powerful analgesics. All of these may cause addiction similar to that produced by morphine. These classes are: (1) Morphine group (morphine, codeine, Dilaudid, heroin); (2) Morphinan group (levorphan)[12]; (3) Meperidine group (Demerol, Nisentil)[2]; (4) Methadone group (methadone, isomethadone)[13]; and (5) Dithienylbutenylamine group.[14] These drugs are used therapeutically chiefly for the effects they produce within the central nervous system, where they affect all levels of integration to varying degrees.[15]

The mechanism of the most important therapeutic effect, the relief of pain, is not fully understood. It appears established that, in man, elevation of the threshold for perception of "quick pain" plays no role. Hill and co-workers[16-18] have shown experimentally in man that one of the important mechanisms through which narcotics exert analgesic action is the reduction of anxiety associated with anticipation of pain.

Addiction to narcotic drugs is characterized by three phenomena: tolerance, physical dependence, and emotional or psychologic dependence (habituation). The latter will be discussed under personal factors.

Tolerance is a diminishing effect on repeated administration of the same dose of a drug, or, conversely, a need to increase the dose on repeated administration in order to obtain the original effect. During continuous use, tolerance to the toxic, sedative, and analgesic effects can become almost complete.

Physical dependence is defined as an altered physiologic state brought about by repeated administration of a drug. This altered state becomes manifest as a characteristic illness, termed an abstinence syndrome, when administration of a drug is suddenly terminated and is manifested by the signs of autonomic hyperactivity, to be enumerated later.

How soon does physical dependence on a narcotic analgesic develop? Observations on the development of physical dependence under conditions of medical use are beset with great difficulties and are considered unreliable.[2] Under conditions of experimental readdiction in man (healthy postaddicts), a morphine abstinence syndrome can be demonstrated by abrupt withdrawal of the drug as early as sixteen days after the beginning of regular administration of 15 to 30 mg. of morphine four times daily. After injection of N-allylnormorphine, an opiate-antagonist, clear-cut opiate "abstinence syndromes" have been induced in sub-

jects who had received 15 mg. of morphine, 15 mg. of heroin, or 10 mg. of methadone four times daily for as short a period as two or three days. These observations indicate that the processes responsible for physical dependence on morphine, methadone, and heroin develop very early during addiction.[19]

The idea that physical dependence is wholly of "psychogenic," that is, of psychologically symbolic, origin still persists despite formidable and conclusive evidence to the contrary.[2] Physical dependence on morphine can be produced in either monkeys or dogs in which "purposive"—i.e., drug-seeking—abstinence changes are never observed after withdrawal. Physical dependence on morphine has been demonstrated in dogs without neocortex and in man after frontal lobotomy. A definite group of changes can be observed in the paralyzed hindlimbs of addicted chronic spinal dogs or addicted spinal man.[15,20]

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Personal and Situational Factors.—Abnormalities of personality structure have been demonstrated in the majority of narcotic addicts. These abnormalities have been handled descriptively[3,9] and have been formulated in psychoanalytic terms.[10] In both approaches, the occurrence of addiction is attributed to the personality defect—to a preaddiction impulse to use drugs. The particular type of drug used is regarded as unimportant and its choice accidental.

Wikler[8,11] has developed a third formulation, called "pharmacodynamic." This formulation, rather than presupposing that the drug used is of no importance, states that specific drugs have specific effects which may be of specific value to individuals with specific psychologic needs, when they receive the drug under suitable circumstances. Opiates are known to produce relief of pain and gratification of hunger and of sexual urges. Aggressive and antisocial impulses are also diminished and passivity is accentuated. Thus, it is thought that addicts are individuals in whom the chief sources of anxiety are related to expression of aggression, fear of pain, and sexuality, regardless of the kind of personality classification used in describing them. The pharmacologic effects of the narcotics are directly valuable to such individuals. Whether or not the patient experiences unusual well-being ("euphoria") would depend to a great extent on the intensity of the needs which the narcotic satisfies specifically. These needs, in turn, would vary in their respective intensities at different moments in the life history of the patient. During illness, dependency needs and self-centeredness are accentuated in association with distress or pain. The administration of narcotics produces a sense of well-being related to the gratification of these needs. This is the desired clinical result. Upon recovery, most patients will remember this well-being with gratitude, but except for such needs as arise with sickness and pain, the effects of narcotics are unnecessary to them since they have been able to achieve contentment before, through socially acceptable channels, through work, play, marriage, etc. Such persons are not apt to become addicts. Some individuals, however, may keenly remember this feeling of gratification as one they had never experienced previously and thus will have strong incentive to seek repeated drug use. These are potential addicts. As the addiction process proceeds, the development of physical dependence creates a new biologic need. The satisfaction of this new need is relatively simple and is directly and intensely pleasurable. It provides the new addict with an attainable, recurring goal for his daily activities. As previously described, physical dependence is a

process which begins early during regular administration of analgesic doses of narcotics. The development of physical dependence appears to serve psychologic purposes. It is more than a coincidence that confirmed narcotic addicts invariably prefer the drugs which produce the most intense physical dependence.

It will be noted that no preaddiction impulse to use drugs is postulated in the "pharmacodynamic" formulation. In fact, exposure to drugs is quite accidental. In the medical setting, it depends primarily on the physician's decision to administer narcotics. Regardless of all other factors, it is clear that there would be no opiate addiction if the first dose of narcotic were not given.

DIAGNOSIS OF ADDICTION

In conformity with the foregoing, the diagnosis of narcotic addiction involves the demonstration of an abstinence syndrome. In cases where physical dependence is established, the diagnosis is based on the occurrence of the nonpurposive abstinence phenomena which are readily observable and not markedly influenced by uncontrollable environmental factors. After abrupt termination of administration of any narcotic, the abstinence syndrome which ensues conforms to a general pattern although the time course and the relative intensities of certain abstinence manifestations vary with the individual narcotics. The prototype narcotic is morphine. After abrupt withdrawal of morphine, the fully developed abstinence syndrome consists of yawning, restlessness, lachrymation, rhinorrhea, sweating, pupillary dilatation, muscle twitches, piloerection (forearms, axillary region, and abdomen), tachypnea, tachycardia, hypertension, nausea, vomiting, and diarrhea. There is insomnia, anxiety, and weight loss; ejaculations occur in men and orgasms in women. The first abstinence changes appear sixteen to twenty hours after abrupt withdrawal of morphine; they reach peak intensity between the forty-eighth and seventy-second hour and subside rapidly during the next five to ten days. Thereafter, minimal abstinence changes may persist for three to six months. Convulsions and delirium do not occur following the withdrawal of narcotics.

The syndromes of abstinence from Dilaudid and heroin are similar except that the abstinence phenomena appear earlier, reach their peak intensities sooner, and subside more rapidly. Withdrawal of codeine causes milder symptoms than morphine withdrawal. The same is true for methadone, but the abstinence syndrome is more prolonged.

Abstinence from meperidine presents distinctive features. Among the withdrawal phenomena, restlessness is extreme, muscular twitching and aching are more prominent. Abstinence changes may appear within two hours after the last injection and drive the user to increase the frequency and the dosage of meperidine. At a daily dose of approximately 3.0 Gm., direct toxic effects of the drug in the form of myoclonic jerks and generalized convulsions may be superimposed on the abstinence phenomena.

The possibility of physical dependence should be considered in any patient who has received narcotics regularly for periods upward of two to four weeks. In addition, in any patient who is observed to experience unusual psychologic well-being following the first few doses of a narcotic, the possibility of developing emotional dependence should seriously be entertained, even though physical dependence might not yet be established.

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TREATMENT OF THE PATIENT MEDICALLY ADDICTED TO NARCOTICS

There is good reason to believe that among patients who become addicted during treatment for illness, a number would accept withdrawal from narcotics without displaying "purposive" abstinence behavior. These would be persons who have developed adequate, socially accepted means of gratifying their "primary" needs and of acquiring contentment. Among so-called "neurotic" individuals, those with aggressive, controlling personalities, or those with obsessive-compulsive traits actually find engendered passivity disagreeable, as it deprives them of their customary patterns of adaptation. These persons would welcome withdrawal of drugs. In most medically addicted persons, the social condemnation of opiate addiction remains an effective motivation, while the factors of association with other addicts and of contact with illegitimate suppliers of narcotics are absent.

On his part, the physician has the same continuing responsibility to his patients for the treatment of medically induced narcotic addiction as he would assume in cases of other therapeutic complications. To dismiss a patient from one's care, soon after realizing that he is addicted, is physiologically and psychologically unjustifiable. It is also socially indefensible, since each addict is a potential focus of infection of other persons in the population. Planned withdrawal from narcotics should be attempted after informing the patient that it is a relatively brief, uncomfortable yet painless, and definitely self-limited period. Chronic illness should not be regarded as an indication for the continued administration of narcotic drugs. Even in the presence of essentially irreversible chronic illness, withdrawal from narcotics may be accomplished safely if it is done gradually,[6] either by progressive withdrawal of the drug of addiction or by the methadone substitution method. The latter is recommended in cases of meperidine addiction. The withdrawal procedures have been described in detail by Wikler,[8] and more recently by Isbell.[1]

PREVENTION OF ADDICTION DURING MEDICAL USE OF NARCOTICS

It is clearly not possible for the practicing physician to carry out personality studies on his patients prior to administration of narcotics, the more so since these drugs are often given under emergency conditions. On the other hand, as shown above, pharmacologic dependence may result from as little as one or two injections of a narcotic, if the injections happen to be given to a person with the specific psychologic needs at a time in his life when these needs are particularly disturbing.

Two principles, if adhered to, will reduce the likelihood of addiction: (1) the patient should not know that he is receiving a narcotic; (2) *a narcotic should never be administered when another medicament will accomplish the same purpose.*

Cases presenting absolute indications for the use of narcotics are those of acute, severe pain. In these, the smallest dose of narcotic sufficient to produce the desired effect should be given. If repeated doses are required, the narcotic should be administered at irregular intervals and not by the clock. The narcotic should be discontinued as soon as severe pain subsides, and nonnarcotic analgesics substituted.

The routine preoperative administration of narcotics is best restricted to patients in pain. In surgical patients not experiencing pain, a small parenteral dose of pentobarbital (90 mg.) can substitute effectively for 15 mg. of morphine as preanesthetic medication.[21] Postoperative administration of narcotics is another routine which should be replaced by individual prescription. It is known that over one-third of unselected patients on general surgical wards experience no significant postoperative pain.[22] Their discomfort can be cared for by methods not requiring narcotics. If narcotics are employed postoperatively, the doses should be spaced irregularly and administration limited to the first one to three days.

Special caution should be exercised in administering narcotics to certain types of patients. Chief among these is the chronic alcoholic, a person who is already practicing pharmacologic self-treatment for personal difficulties. The ready availability of alcohol may be the principal factor in his choice of addicting drug. In fact, significant numbers of opiate addicts are former alcoholics who underwent sudden and irrevocable conversion to narcotics after their first exposure to these drugs, often at the hands of physicians. Other types of patients requiring similar circumspection are those with multiple operations, and those whose complaints are markedly out of proportion to the physical findings. Narcotics are not the proper means of alleviating distress resulting from emotional conflict.

The administration of narcotics to a patient with chronic pain is merciful, but merely on a short-term basis. Tolerance soon develops to the analgesic effects of the drug and alleviation of pain becomes inadequate in spite of high dosage. Withdrawal of narcotics at this point does not deprive the patient of any actual benefit but protects him and his family from the legal, social, and economic difficulties attendant on opiate addiction.

Clinically, the distinction of organic pain from psychogenic pain cannot be sustained and should be discarded. In the final analysis, pain is a psychic phenomenon, no matter how tangible its source of origin. It is invariably both a sensory and an emotional experience. Factors affecting any aspect of this whole will modify the total experience. In meeting the challenge of pain, acute or chronic, management should be directed simultaneously at several aspects of the total experience. A major factor in the management of pain is the performance of the physician. If he regards pain traditionally as merely a symptom of physical disease, he disregards the emotional changes that arise with pain (such as increased dependency needs) and fails to utilize the relationship between himself and his patient in helping the patient adapt to pain. Such a physician finds it necessary to administer narcotics frequently. Because he offers nothing else, he tends to make the use of narcotics essential to his patients. On the other hand, the attentive physician who is able to offer his patients steady support and realistic perspective obtains similar results while resorting infrequently to the use of narcotics. The validity of this statement has been observed in several medical institutions. At the Montreal Neurological Institute, perhaps originally by extension of the neurosurgical necessity of avoiding opiates in cranial cases, the use of narcotics in cases of laminectomy and vertebral trauma has been mini-

mal for many years. The patients' treatment takes place in an atmosphere characterized by a realistic approach to their medical and surgical problems, by skilled, effective nursing care, and by cordiality and mutual confidence between attending, house, and nursing staffs. In such a setting, it is possible to allay preoperative anxiety and to manage postoperative pain principally with nonnarcotic analgesics, sedatives, and physiotherapy, as indicated. Similar observations on the relation of the intensity of postoperative pain in relation to the patient's hospital setting have been reported by Papper and his associates.[22]

SUMMARY AND CONCLUSIONS

Until such time as a potent, nonaddicting analgesic is found, constant care and discrimination must be exercised by the physician administering narcotic analgesics. In the foregoing survey, an attempt has been made to present data toward a rational basis for the prevention of addiction during effective utilization of the narcotic analgesics. While it is no longer necessary to postulate a preaddiction impulse to use drugs, it appears that drug addiction may develop when individuals with specific psychologic needs are exposed to opiatelike drugs whose specific effects may be particularly valuable to them under suitable circumstances. Attention is called to the fact that the processes of pharmacologic dependence (both physical and emotional) develop very early during the regular administration of analgesic doses of narcotics. Since it is usually not possible to identify individuals possessing the particular psychologic needs which may make them susceptible to narcotic addiction, the physician is urged to hold to a minimum the administration of narcotics in everyday practice.

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